National Toxicology Program

U.S. Department of Health and Human Services

Annual Report 2008

National Toxicology Program

ANNUAL REPORT
For
Fiscal Year 2008

National Institute of Environmental Health Sciences
National Institutes of Health

National Center for Toxicological Research
Food and Drug Administration

National Institute for Occupational Safety and Health
Centers for Disease Control and Prevention

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Department of Health and Human Services
National Toxicology Program
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Frequently Used Abbreviations

ACB	allele-specific competitive blocker
ACVP	American College of Veterinary Pathologists
ADME	absorption, distribution, metabolism, and excretion
AHS	Agricultural Health Study
ATSDR	Agency for Toxic Substances and Disease Registry
ACVP	American College of Veterinary Pathologists
AZT	Zidovudine
BCOP	Bovine Corneal Opacity and Permeability
Be	beryllium
BPA	bisphenol A
BRD	background review document
BSC	Board of Scientific Counselors
Cd	cadmium
CDC	Centers for Disease Control and Prevention
CERHR	Center for the Evaluation of Risks to Human Reproduction
CMPB	Cellular and Molecular Pathology Branch
CNT	carbon nanotube
COX	cyclooxygenase
CPM	counts per minute
CPSC	Consumer Product Safety Commission
CYP	cytochrome P450
DEHP	di(2-ethylhexyl) phthalate
DEP	diesel exhaust particles
DHHS	Department of Health and Human Services
DIR	Division of Intramural Research
DNMT	DNA methyltransferases
DOD	Department of Defense
DOE	Department of Energy
ECVAM	European Centre for the Validation of Alternative Methods
EPA	Environmental Protection Agency
ER	estrogen receptor
FDA	Food and Drug Administration
FOB	functional observational battery
FY 2008	fiscal year 2008
GABA	gamma-aminobutyric acid
GAC	Genetic Alterations in Cancer database
GMM	genetically modified model
GST	glutathione-S-transferase
HELD	Health Effects Laboratory Division (NIOSH)
HF/LC	high fat/low carbohydrate
HMA	human microbiota-associated
HRT	hormone replacement therapy
HTS	high throughput screening
IARC	International Agency for Research on Cancer
ICATM	International Cooperation on Alternative Test Methods
ICE	Isolated Chicken Eye
ICCEC	Interagency Committee for Chemical Evaluation and Coordination
ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
IL	interleukin
IRIS	Integrated Risk Information System
ITC	Interagency Testing Committee
JaCVAM	Japanese Center for the Validation of Alternative Methods

LC/MS	liquid chromatography-mass spectrometry
LLNA	Local Lymph Node Assay
LOX	lipoxygenase
LTB4	leukotriene B4
MALT	mucosal-associated lymphoid tissues
MDIG	mineral dust-induced gene
Mn	manganese
MWF	metal working fluid
NAT	N-acetyltransferase
NCI	National Cancer Institute
NCP	NTP Center for Phototoxicology
NCTR	National Center for Toxicological Research
NCEH	National Center for Environmental Health
NICEATM	NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
NHGRI	National Human Genome Research Institute
NICHD	National Institute of Child Health and Human Development
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NIST	National Instititute of Standards and Technology
NLM	National Library of Medicine
NMDA	N-methyl-D-aspartic acid
NOS	nitric oxide synthase
NR	NMDA receptor
NTP	National Toxicology Program
OECD	Organisation for Economic Cooperation and Development
OLPR	Office of Liaison, Policy and Review
ONS	Office of Nomination and Selection
OPA	orthophthalaldehyde
OSHA	Occupational Safety and Health Administration
PGE	prostaglandin
PBPK	physiologically-based pharmacokinetic
PBPK/PD	PBPK/pharmacodynamic
PCR	polymerase chain reaction
PPAR	peroxisome proliferator-activated receptor
PWG	pathology working group
RACB	reproductive assessment by continuous breeding
RoC	Report on Carcinogens
ROS	reactive oxygen species
RPT	rabbit pyrogen test
SACATM	Scientific Advisory Committee on Alternative Toxicological Methods
STP	Society of Toxicologic Pathologists
SULT1A1	sulfotransferase 1A1
TiO_2	titanium dioxide
TMA	trimilletic anhydride
TR	Technical Report
TRRS	Technical Reports Review Subcommittee
TXA2	thromboxane A2
TZD	glitazones
UV	ultraviolet
US	United States

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Letter from the NTP Associate Director

In 2008 the National Toxicology Program (NTP) celebrated its 30th anniversary as a leader in the effort to apply the science of toxicology to the protection of public health. During its history, the NTP has studied > 2,500 substances for toxicity and/or carcinogenicity and provided critical information used by health regulatory and research agencies. In meeting its challenge today, the NTP is committed to (a) maintaining our traditional areas of strength in toxicology research and testing, (b) accelerating our efforts to fulfill the goals set forth in *A National Toxicology Program for the 21st Century: A Roadmap for the Future* (NTP, 2004), and (c) exploring new scientific opportunities to understand how individual genetic susceptibilities affect responses to environmental exposures.

The NTP's strength continues to be the collective activities of its agency partners – the CDC's National Institute for Occupational Safety and Health (NIOSH), the National Center for Toxicological Research (NCTR) of the Food and Drug Administration (FDA), and the National Institute of Environmental Health Sciences (NIEHS) at the National Institutes of Health (NIH). The NTP has had an eventful and productive FY 2008, starting with a realignment of the NIEHS program within the Division of Intramural Research, with the goal of providing a clearer identity to activities, staff, and dollars associated with the NTP through this consolidation. The new NTP at the NIEHS brings together the staff working on public health issues and nominated substances, those carrying out the important analysis activities to produce the Report on Carcinogens and the Center for the Evaluation of Risks to Human Reproduction monographs, and those who support the Interagency Coordinating Committee on the Validation of Alternative Methods. The NTP has expanded in two important areas by creating new branches at the NIEHS. The Biomolecular Screening Branch is the home for activities related to the applicability and utility of rapid-throughput assays for toxicology. The Host Susceptibility Branch will conduct research aimed at improving our understanding of the genetic bases for differential responses to environmental insults.

A number of interagency collaborations ensued this year including a memorandum of understanding with the National Human Genome Research Institute's NIH Chemical Genomics Center and the U.S. Environmental Health Agency (EPA) National Center for Computational Toxicology ToxCast™ program and another with the EPA for a phthalate initiative. Another important activity was the drafting of new levels of evidence criteria, patterned after the NTP carcinogenicity criteria, to evaluate findings from NTP immuntoxicology and reproductive and developmental toxicology studies.

The NTP continues to focus on public health issues and concerns such as evaluating the potential adverse effects of exposures to cellular phone radiation emissions, nanoscale materials, DNA-based therapies, dietary supplements, phototoxicants, occupationally-relevant substances, and mold. With these efforts, NTP continues to work with our agency partners and our scientific advisory boards to remain at the cutting edge of scientific research to address our public health mission.

John R. Bucher, Ph.D.

Overview of the National Toxicology Program

Mission and Goals

Currently, the Toxic Substances Control Act Chemical Substance Inventory (*http://www.epa.gov/oppt/newchems/pubs/invntory.htm*), first published in 1979, lists over 80,000 chemicals as being available for sale and use in the United States. Approximately 850 active pesticide ingredients are formulated into approximately 17,000 pesticide products. An estimated 500-600 new industrial chemicals are introduced annually into US commerce. The effects of many of these substances on human health are unknown, yet people and our environment may be exposed to them during their manufacture, distribution, use, and disposal or as pollutants in our air, water, or soil. While relatively few substances are thought to pose a significant risk to human health, safeguarding the public depends upon identifying the effects of these agents as well as certain naturally occurring chemicals, and determining the levels of exposure at which they may become potentially hazardous to humans.

NTP MISSION:

To evaluate agents of public health concern by developing and applying the tools of modern toxicology and molecular biology.

The Department of Health Education and Welfare (now the Department of Health and Human Services, DHHS) established the National Toxicology Program (NTP) in 1978 as a focal point to coordinate toxicology testing in the federal government. In carrying out its mission, the NTP has several goals to:

- provide evaluations of substances of public health concern.
- develop and validate improved (sensitive, specific, rapid) testing methods.
- develop approaches and generate data to strengthen the science base for risk assessment.
- communicate with all stakeholders including government, industry, academia, the environmental community, and the public

Organizational Structure and Oversight

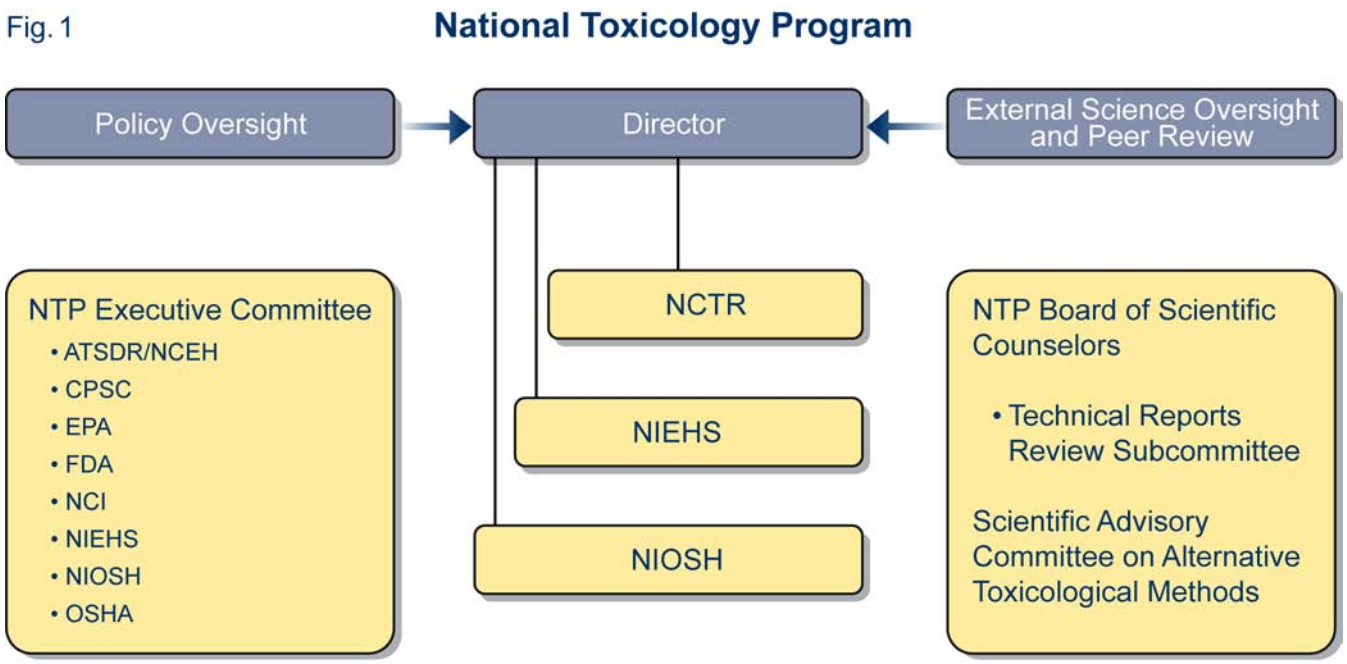
Three agencies, the National Institute of Environmental Health Sciences (NIEHS) at the NIH, the National Institute for Occupational Safety and Health (NIOSH) of the CDC, and the National Center for Toxicological Research (NCTR) of the FDA, form the core for this program (Figure 1). The NTP is located at the NIEHS and the Director of the NIEHS serves as the NTP Director. Questions and inquiries about the NTP can be directed to the NTP Office of Liaison, Policy and Review (919-541-7539) or *CDM@niehs.nih.gov*.

NTP Management during FY 2008

Dr. Samuel Wilson, Acting Director of NIEHS and NTP

Agency Program Management
NCTR: Dr. William T. Allaben, Associate Director for Scientific Coordination
NIEHS: Dr. John Bucher, Associate Director, NTP
NIOSH: Dr. Mark Toraason, Director, Senior Fellow, Division of Applied Research

Fig. 1



Staff of the agencies involved with the program and their contact information are provided in Appendix 1.

Addressing Scientific and Regulatory Needs

The NTP is committed to the concept of "good science for good decisions." This allows the program to be flexible and innovative in its approach toward addressing public health concerns related to exposures to chemical and physical agents at home, in the workplace, and in the environment. The NTP has expanded its scope beyond cancer to include examining the impact of substances on non-cancer outcomes such as those affecting reproduction and development and the immune, respiratory, and nervous systems.

The NTP recognizes that initiatives addressing critical knowledge gaps in toxicological evaluations offer the best opportunities for preventing environmentally mediated diseases. Therefore, the program's testing of substances is evolving to include more mechanism-based toxicology studies that focus on understanding the modes of action of chemical agents. In recent years, the NTP has placed a greater emphasis on providing human relevance to the interpretation and understanding of toxicological

information generated using animal or *in vitro* cell models. This is imperative in order to be at the forefront in research efforts to improve risk assessment methodologies for quantifying the sequence of events that starts with chemical exposure and ends with toxicity.

Examples of activities it covers include:

- The increased application of mechanistic information and scientific judgment in the deliberations for listings in the Report on Carcinogens (RoC).
- An enhanced effort to examine the merits of alternative testing methods that may provide better information than current models using fewer animals, causing less pain or distress, and potentially provide improved data to reduce uncertainties in risk assessments.
- An increased effort to collect information on a broad variety of exposures (either environmental or occupational), mixtures of concern, and life-stage susceptibility.

Nationally, the NTP rodent bioassay is recognized as the standard for identification of carcinogenic agents; however, the NTP continues to work to reduce the use of experimental animals and develop and validate alternative testing methods. This effort led to the creation of NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) in 1998. The NTP will continue to work with the Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM) through NICEATM in promoting the development, validation, and regulatory acceptance of new and revised alternative toxicological methods.

Strengthening existing partnerships and forging new ones are important to achieve NTP goals. Partnerships with sister federal agencies are increasing (Interagency Agreements are presented in the Interagency Agreements section, page 85). The NTP continues to support an effort to evaluate the phototoxicity of various compounds through the NTP Center for Phototoxicology at NCTR. In addition, the NTP is contributing to toxicological assessments of emerging issues such as nanotechnology, radiofrequency radiation emissions from cellular phones, herbal medicines/dietary supplements, and phthalates and will provide this information to other agencies.

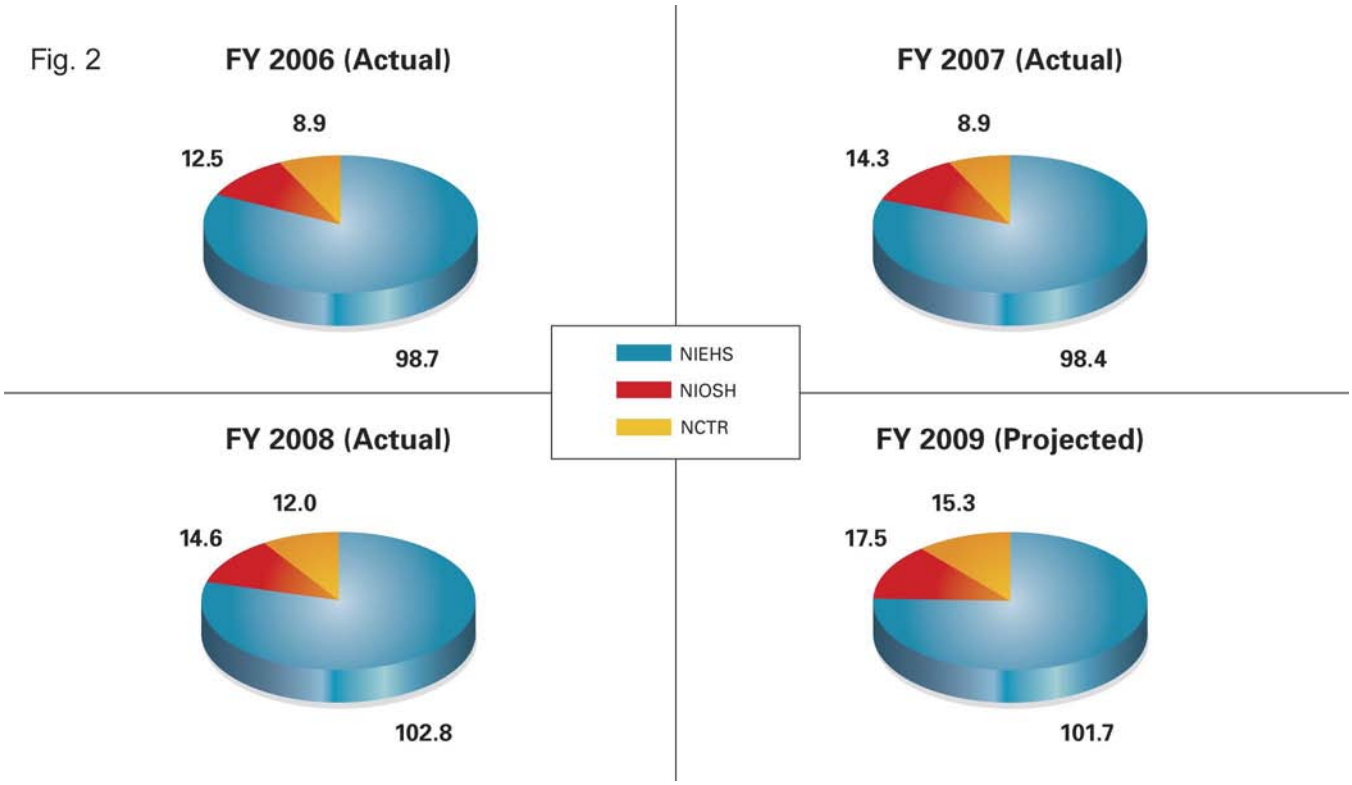
Regulatory agencies make decisions for the protection of public health based on scientific information from multiple sources (e.g., toxicology, human studies, and basic research). The NTP plays a critical role in providing needed scientific data, interpretation, and guidance concerning the appropriate uses of these data to regulatory agencies as well as other groups involved in health-related research. The program is committed to using the best science available in setting priorities for future studies and in designing, conducting, and interpreting the findings of those studies. The American people and government agencies at state and federal levels rely on the NTP to provide a strong scientific basis for making credible decisions that will protect public health. The program maintains an objective, science-based approach in dealing with critical issues in toxicology and is recognized by many groups for its scientific rigor, objectivity, and open approach in the continuing dialogue on the appropriate application of scientific advances to applied toxicology research and testing.

Resources and Planning

Current and Projected Research Capacity

The NTP relies on voluntary allocations from the program's three core agencies (NIEHS, NCTR, and NIOSH) for supporting its various programs and initiatives. These allocations are specified following the determination of yearly appropriations. As shown in Figure 2, the actual allocations from the principals toward the NTP increased slightly from 2007 to 2008 and are projected to provide a total funding level of $134.5 million (direct plus indirect) in FY 2009. The NTP primarily conducts its research studies in-house at the core agencies or through contract laboratories, but also supports interagency agreements with other federal agencies. Funds are used to sponsor workshops and conferences and produce and disseminate printed programmatic materials. In FY 2008, the NIEHS funded 36 contracts and sponsored 3 workshops and 7 expert panel meetings for the NTP. In addition, NIEHS funded interagency agreements with NIOSH, NCTR, EPA, and NCGC.

Fig. 2



The NTP maintains an objective, science-based approach in dealing with critical issues in toxicology and continually sets priorities to improve the nation's ability to evaluate human health effects from environmental exposures.

In totality, the NTP is a comprehensive interagency research program whose core agencies are committed to providing resources to support the program's research efforts and for communicating the knowledge learned to all stakeholders, public and private. The program's testing, research, and health hazard assessment efforts are directed toward obtaining the best scientifically valid data that can be used by health regulatory and research agencies for making appropriate decisions about potential human risk(s) from exposure to environmental toxicants. Toward that end, the NTP is continually evolving to remain at the cutting edge of scientific research and the development and application of technology.

Advisory Boards and Committees

NTP Board of Scientific Counselors

The NTP Board of Scientific Counselors (BSC), a federally chartered advisory group, provides scientific oversight to the program including its centers, the RoC, and Center for Evaluation of Risks to Human Reproduction (CERHR). The Secretary of Health and Human Services appoints members to the BSC. The BSC can be composed of up to 35 scientists, primarily from the public and private sectors with scientific expertise relevant to the NTP's activities. The BSC members serve rotating terms of up to four years and the BSC typically meets two times per year. The BSC's Technical Reports Review Subcommittee (TRRS) generally meets once a year and provides peer review of draft NTP technical reports on long-term toxicology and carcinogenesis studies. The BSC is managed by the NTP Executive Secretary Dr. Barbara Shane. A list of members during FY 2008 is provided in Table 1.

BSC meetings in FY 2008

The BSC met December 6, 2007, at the NIEHS in Research Triangle Park, NC. The BSC heard a report on NTP study plans for mold. The BSC and *ad hoc* reviewers provided input on NTP-proposed study concepts for nominations to the testing program: aminopyridines, diethyl phthalate, 2-methoxy-4-nitroaniline, nanoscale gold, 2',2'-dithiobisbenzanilide, pentaethylenehexamine, and a phthalates initiative. The chair of the TRRS presented the subcommittee's recommendations from its peer review of six draft NTP Technical Reports and one multigenerational study from the meeting held in May 2007. The BSC unanimously accepted the subcommittee's recommendations for the draft reports. BSC provided input and voted on two proposed nominations, lead and cadmium, for evaluation by CERHR. The BSC heard reports on the process and timelines for preparing the 12th Report on Carcinogens and for implementing recommendations from NTP workshops and a retreat.

The second FY 2008 meeting of the BSC was held on June 11-12, 2008, at the Radisson Hotel in Research Triangle Park, NC. The BSC, supplemented with *ad hoc* scientific experts, peer-reviewed the draft NTP Brief on Bisphenol A (BPA). Overall, the BSC agreed with the NTP conclusions on BPA expressed in the draft brief, but recommended a lower level of concern for effects on the mammary gland and age of puberty in females. The BSC and other *ad hoc* reviewers provided input to the NTP on proposed study concepts for six nominations to the testing program: 2,2'-dimorpholinodiethyl ether, 2-ethylhexyl-*p*-methoxycinnamate, tetravalent and pentavalent vanadium compounds, 4,7,10-trioxatridecane-1,13-diamine, furan, and melamine and cyanuric acid. The BSC reviewed and approved a concept for a contract to provide research support to the NTP. The chair of the TRRS presented the subcommittee's recommendations from its peer-review of six draft NTP Technical Reports, one photocarcinogencity study, and one draft NTP Toxicity Report peer-reviewed at the meeting on February 27-28, 2008. The BSC unanimously accepted the subcommittee's recommendations for the draft reports. The BSC heard a presentation on the proposed development of criteria for evaluating outcomes in reproductive and developmental toxicology studies and immunotoxicology studies and the progress that had been made on the Host Susceptibility Program.

TRRS meetings in FY 2008

The TRRS met in public forum on February 27-28, 2008, at the NIEHS. The subcommittee peer-reviewed the findings and conclusions of six draft NTP Technical Reports that used conventional rodent models, one photocarcinogencity study, and one draft NTP Toxicity Report. The subcommittee's recommendations were reported to the BSC at the June 2008 meeting.

BSC Working Group meetings in FY 2008

Two BSC working groups were convened to evaluate the suitability and utility of specific draft criteria for describing the results from individual NTP immunotoxicology, reproductive toxicology, and developmental toxicology studies to indicate the strength of the evidence for their conclusions. The Immunotoxicology Working Group meeting was held on August 13-14, 2008, in Crystal City, VA and the Reproductive and Developmental Toxicology Working Group met on September 10-12, 2008, at the Hilton Garden Inn, Durham, NC. These meetings were not open to the public. Both groups prepared reports on their deliberations, which included recommended changes to the draft criteria, that were presented at the November 2008 BSC meeting.

Additional information about the BSC, including minutes from its meetings, are accessible on the NTP website (*http://ntp.niehs.nih.gov/* select "Advisory Board and Committees") or from Dr. Barbara S. Shane, Executive Secretary, NIEHS (*shane@niehs.nih.gov*).

Table 1. NTP Board of Scientific Counselors Membership Roster FY 2008

Name and Title	Affiliation	Term Ends	BSC Service
Christopher Bradfield,Ph.D. Professor of Oncology	McArdle Laboratory for Cancer Research, Madison, WI	06/30/08	BSC and TRRS
Tracie E. Bunton, D.V.M., Ph.D., DACVP Toxicology Consultant	Eicarte LLC Fairfield, PA	06/30/10	BSC and TRRS
Edward W. Carney, Ph.D. Technical Leader, Developmental, Reproductive & General Toxicology	The Dow Chemical Company Midland, MI	06/30/10	BSC
Russell C. Cattley, V.M.D., Ph.D. Executive Director Pathology	Amgen Thousand Oaks, CA	06/30/10	BSC and TRRS
Kenny S. Crump, Ph.D. Research Professor	Louisiana Tech University Ruston, LA	12/27/08	BSC and TRRS
George Friedman-Jiménez, M.D. Assistant Professor	New York University School of Medicine New York, NY	06/30/09	BSC
S. Katherine Hammond, Ph.D., CIH Professor of Public Health	University of California – Berkeley Berkeley, CA	12/27/09	BSC
William P. Janzen Professor, Division of Medicinal Chemistry and Natural Products Director, Assay Development and Compound Profiling	University of North Carolina at Chapel Hill Chapel Hill, NC	06/30/10	BSC
Nancy I. Kerkvliet, Ph.D. Professor, Immunotoxicology and Extension Toxicologist Specialist	Oregon State University Corvallis, OR	12/27/08	BSC and TRRS
Jane Koenig, Ph.D. Professor, Environmental and Occupational Health Sciences	University of Washington Seattle, WA	12/30/08	BSC
D. Gail McCarver, M.D. (chair) Co-Director, Department of Pediatrics	Medical College of Wisconsin Milwaukee, WI	12/27/08	BSC
Jon C. Mirsalis, Ph.D. Managing Director, Biosciences Division	SRI International Menlo Park, CA	12/27/08	BSC and TRRS
Raymond F. Novak, Ph.D. Director, Institute of Environmental Health Sciences	Wayne State University Detroit, MI	06/30/10	BSC and TRRS
Michael V. Pino, D.V.M., Ph.D. Director of Pathology	Sanofi-Aventis Bridgewater, NJ	06/30/09	BSC and TRRS

Name and Title	Affiliation	Term Ends	BSC Service
Kenneth M. Portier, Ph.D. Director of Statistics	American Cancer Society Atlanta, GA	06/30/09	BSC and TRRS
Jim E. Riviere, D.V.M., Ph.D., A.T.S. Burroughs Wellcome Fund Distinguished Professor of Pharmacology	North Carolina State University Raleigh, NC	06/30/09	BSC and TRRS
Diane M. Robins, Ph.D. Professor	University of Michigan Medical School Ann Arbor, MI	06/30/09	BSC
Keith A. Soper, Ph.D. Senior Director, Biometrics Research	Merck West Point, PA	12/27/08	BSC and TRRS
David H. Wegman, M.D., MSc Dean	University of Massachusetts Lowell, MA	06/30/09	BSC

Scientific Advisory Committee on Alternative Toxicological Methods

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) is a federally chartered advisory committee established on January 9, 2002, in response to the ICCVAM Authorization Act of 2000 (42 U.S.C. 285*l*-3(d)). SACATM advises the ICCVAM, the NICEATM, and the Director of the NIEHS regarding statutorily-mandated duties of ICCVAM and activities of NICEATM (see page 48). SACATM provides advice on priorities and activities related to the development, validation, scientific review, regulatory acceptance, implementation, and national and international harmonization of new, revised, and alternative toxicological test methods. Alternative methods are those that reduce, refine (lessen or avoid pain and/or distress), or replace the use of animals in testing. SACATM also provides input on ways to foster partnerships and communication with interested parties. The NIEHS Director appoints 15 voting members to the SACATM, and membership as defined in the ICCVAM Authorization Act of 2000 includes representatives drawn from academia, state government, industry, and animal protection organizations (Table 2). Members serve rotating terms of up to four years. SACATM typically meets once a year. SACATM is managed by the NTP Executive Secretary Dr. Lori White.

SACATM met on June 18 – 19, 2008, at the Radisson Hotel Research Triangle Park in Research Triangle Park, NC. At the meeting, SACATM discussed one nomination, the NTP Rodent Bioassay for Carcinogenicity. SACATM voted to concur with ICCVAM's recommended low priority for the nomination. SACATM heard overviews of the National Research Council Report on *Toxicity Testing in the 21st Century* and the NICEATM-ICCVAM Five-Year Plan. Six federal agencies provided updates of their research, development, translation, and validation activities relevant to the NICEATM-ICCVAM Five-Year Plan. SACATM provided comments on (1) the independent scientific peer review validation status of the murine Local Lymph Node Assay for assessment of the contact dermatitis potential of chemicals and products and (2) the scientific workshop on Acute Chemical Safety Testing: Advancing *In Vitro* Approaches and Humane Endpoints for Systemic Toxicity Evaluations. SACATM was provided updates on NICEATM-ICCVAM activities and on the regulatory acceptance and availability of ICCVAM-recommended alternative test methods. Liaisons from the European Center for the Validation of Alternative Methods and the Japanese Center for the Validation of Alternative Methods presented updates on the activities of their groups.

Additional information about SACATM, including minutes from its meetings, is available on the NTP website (*http://ntp.niehs.nih.gov/* select "Advisory Board and Committees") or from Dr. Lori White, Executive Secretary, NIEHS (*whiteld@niehs.nih.gov*).

Table 2. Scientific Advisory Committee on Alternative Toxicological Methods Roster FY 2008		
Name and Title	**Affiliation**	**Term Ends**
Frank Barile, Ph.D. Associate Professor	St. John's University Jamaica, NY	06/30/09
Richard A. Becker, Ph.D. Senior Director	American Chemical Council Arlington, VA	06/30/08
June A. Bradlaw, Ph.D. Science Advisor	International Foundation for Ethical Research Rockville, MD	06/30/08
Marilyn J. Brown, D.V.M. Executive Director, Animal Welfare and Training	Charles River Laboratories East Thetford, VT	06/30/09
Grantley D. Charles, Ph.D. Senior Scientist, Toxicology	Allergan Irvine, CA	06/30/09
Mary Jane Cunningham, Ph.D. Program Manager	Integrated Laboratory Systems Durham, NC	06/30/08
George DeGeorge, Ph.D. Director of Toxicology	MB Research Laboratories Spinnerstown, PA	06/30/08
Helen E. Diggs, D.V.M. Associate Dean, Hospital Program Director Veterinary Teaching Hospital	College of Veterinary Medicine, Oregon State University Corvallis, OR	06/30/10
Michael Dong, Ph.D. Staff Toxicologist	California Department of Pesticide Regulation Sacramento, CA	06/30/08
Marion F. Ehrich, Ph.D. Professor, Biomedical Sciences and Pathology/Laboratory for Neurotoxicity Studies	University of Washington Seattle, WA	06/30/10
Donald A. Fox, Ph.D. Professor, Pharmacological and Pharmaceutical Sciences	University of Houston Houston, TX	06/30/09
James Freeman, Ph.D. (chair) Distinguished Toxicology Associate	ExxonMobil Biomedical Sciences, Inc. Annandale, New Jersey	06/30/10
Daniel S. Marsman, D.V.M., Ph.D. Section Head, Animal Welfare and Alternatives	Procter and Gamble Cincinnati, OH	06/30/09
Roger O. McClelllan, D.V.M. Consultant	Albuquerque, NM	06/30/08
Annie (Peiyong) Qu, Ph.D. Associate Professor, Department of Statistics	University of Illinois at Urbana-Champaign Champaign, IL	06/30/10

NTP Executive Committee

The NTP Executive Committee provides programmatic and policy oversight to the NTP Director. The Executive Committee meets once or twice a year in closed forum. Dr. John Howard, NIOSH, serves as chair of the Executive Committee. Members of this committee include the heads (or their designees) from the following federal agencies:

- Agency for Toxic Substances and Disease Registry/National Center for Environmental Health
- Consumer Product Safety Commission
- Environmental Protection Agency
- Food and Drug Administration
- National Cancer Institute
- National Institute of Environmental Health Sciences
- National Institute for Occupational Safety and Health
- Occupational Safety and Health Administration

Interagency Committee for Chemical Evaluation and Coordination (ICCEC)

The ICCEC evaluates nominations to the NTP testing program and makes recommendations with respect to both specific types of toxicological studies and testing priorities. Dr. Marilyn Wind, Consumer Product Safety Commission (CPSC), serves as chair of the ICCEC. The ICCEC meets once or twice annually in closed forum and is composed of representatives from:

- Agency for Toxic Substances and Disease Registry/National Center for Environmental Health
- Consumer Product Safety Commission
- Department of Defense
- Environmental Protection Agency
- National Center for Toxicological Research
- National Cancer Institute
- National Institute of Environmental Health Sciences
- National Institute for Occupational Safety and Health
- Occupational Safety and Health Administration

Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)

ICCVAM is a permanent interagency committee of the NIEHS under NICEATM. The committee was formally established in law by the ICCVAM Authorization Act of 2000 (42 U.S.C. 285*l*-3(d)). The purpose of ICCVAM is to establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new or revised scientifically valid toxicological tests that protect human and animal health and the environment while reducing, refining, or replacing animal tests and ensuring human safety and product effectiveness (see *http://iccvam.niehs.nih.gov/about/process.htm*).

Dr. Marilyn Wind, CPSC, serves as chair of ICCVAM. ICCVAM meets several times per year in closed forum. It is composed of representatives from 15 Federal agencies that generate or use toxicological data to carry out their responsibilities to protect and advance the health and safety of people, animals, and the environment:

- Agency for Toxic Substances and Disease Registry
- Consumer Product Safety Commission
- Department of Defense
- US Department of Agriculture
- Department of Energy
- Department of the Interior
- Department of Transportation
- Environmental Protection Agency
- Food and Drug Administration
- National Cancer Institute
- National Institute of Environmental Health Sciences
- National Institutes of Health
- National Institute for Occupational Safety and Health
- National Library of Medicine
- Occupational Safety and Health Administration

NIOSH/NTP

NIOSH/NTP: Division of Applied Research and Technology

NIOSH/NTP: Division of Surveillance, Hazard Evaluations, and Field Studies

NIOSH/NTP: Health Effects Laboratory Division

The National Institute for Occupational Safety and Health (NIOSH) is the federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness. The mission of the NIOSH is to generate new knowledge in the field of occupational safety and health and to transfer that knowledge into practice for the betterment of workers. To accomplish this mission, NIOSH conducts scientific research, develops guidance and authoritative recommendations, disseminates information, and responds to requests for workplace health hazard evaluations.

NIOSH's participation in the NTP is consistent with its mandate to protect workers' health and safety under the Occupational Safety and Health Act and the Federal Mine Safety and Health Act. Setting priorities in occupational toxicological research is based upon a variety of information sources developed and maintained by NIOSH, including: Health Hazard Evaluations, industry-wide studies, gaps in knowledge identified through the development of criteria for recommended standards or Criteria Documents, Current Intelligence Bulletins, hazard reviews or alerts, and other technical reports, and information profiles on chemical hazards. Toxicological research on important occupational chemicals is conducted in cellular and genetic toxicology, carcinogenesis research and testing, toxicologic characterization, chemical disposition, neurobehavioral toxicology, reproductive and developmental toxicology, dermal toxicology, and exposure assessment.

NIOSH research projects are conducted by the Division of Applied Research and Technology (DART) and by the Division of Surveillance, Hazard Evaluations, and Field Studies (DSHEFS) located in Cincinnati, Ohio, and by the Health Effects Laboratory Division (HELD), located in Morgantown, West Virginia. NIOSH/NTP studies funded by NIOSH voluntary allocations are listed in Table 3.

Table 3: NIOSH/NTP Projects FY 2008*	
NIOSH/NTP Project [Project Officer]	**Objective and Project Summary**
Biomarker Development for Field Studies *[B'Hymer]*	To provide the biomonitoring analyses required for field investigations of occupational exposures. Biomarker methods will be developed and applied for occupational toxicants to assess exposure and susceptibility and will target the manufacturing, service, and healthcare sectors. Efforts continued to study biomarkers of susceptibility as they related to metabolism and DNA repair pathways, with respect to acrylamide and manicurists.
Reproductive Health Assessment of Male Workers *[Schrader]*	To assess reproductive health hazards using a health profile consisting of biomarkers for evaluating male fecundity. Work focused on the Longitudinal Investigation of Fertility and the Environment (LIFE) project, which is a collaborative effort between NIOSH and the National Institute of Child Health and Human Development.
Statistical Research Development and Planning *[Krieg]*	To provide statistical planning and analysis for all research done within the NIOSH Division of Applied Research and Technology. This includes power calculations, the development of study designs, statistical data analyses, and graphs and written reports that summarize the analyses and their results.
Immunochemical Biological Monitoring for Occupational Exposure and Disease *[Striley]*	To evaluate industrial and agricultural chemicals with known acute and chronic toxicities, which present a significant exposure risk for workers. Biological monitoring can assess exposure by analyzing acute and latent metabolites in various biological media. The goal of this project is to develop low-cost, rapid immunochemical and analytical chemistry biomonitoring methods that will be used to identify exposures and evaluate potential interventions. Concurrent with development of exposure assessment methods, this project will identify and develop new multiplex immunochemical methods to evaluate biomarkers of occupational illness or subclinical signs of occupational illness.
Research Development and Planning *[DeBord]*	To provide scientific and administrative oversight for the Biomonitoring and Health Assessment Branch investigative research, methods development and collaborations in biological monitoring and biomarkers, reproductive health assessments, genotoxicity, genetics, immunochemistry and immunotoxicology.
Development of Urinary Metabolite Methods for Biomonitoring *[B'Hymer]*	To develop and validate test methods for quantification of urinary metabolites or parent chemicals that can be used as biomarkers of exposure for various hazardous workplace chemicals. The goal is to analyze archived specimens from various current and past NIOSH project studies. Research activities will be expanded later in the project's time-line as new collaborative studies are developed.
Assessing the Reproductive Health of Female Workers *[Kesner]*	To develop and apply methods to assess reproductive health of women exposed to occupational hazards, help with intervention to lessen hazardous impact, and collaborate globally towards maximizing impact of these goals. Methods development will focus on specific, sensitive measurements of female reproductive hormones and other biological markers of reproductive status in readily collectible body fluids, such as urine and saliva. Initial studies will assess the effects of pesticides, polyhalogenated biphenyls, and metals on women's reproductive health in the agriculture, manufacturing, and mining sectors.
Acrylamide Workers' Reproductive and Neurological Health *[Moorman]*	To determine exposures and potential reproductive and neurobehavioral effects in acrylamide-exposed workers in the manufacturing sector. Sampling and analysis of ambient and personal air levels has been completed, as well as hemoglobin adducts as internal dose markers at a major production facility. The project is also evaluating male workers with and without exposures to acrylamide for exposures and reproductive and neurological endpoints. Exposures are assessed by area and personal sampling, dermal sampling, reported exposure data, and exposure biomarkers.

**Funded by NIOSH voluntary allocations*

NIOSH/NTP Project [Project Officer]	Objective and Project Summary
Orthophthalaldehyde (OPA) Hazard Assessment *[Toraason]*	To assess occupational exposures to OPA and determine if healthcare workers are experiencing adverse effects associated with exposure.To assess exposure, this study will also develop analytical methods for environmental monitoring of OPA and determine the feasibility of an OPA biomarker. Because of the absence of published toxicological data on OPA, testing will be conducted in experimental animals. The toxicological testing will focus on dermal and respiratory irritation and sensitization. Dose-response data will be obtained for hazard identification risk assessment, which, along with health assessments, will serve as the basis for establishing exposure limits.
Manicurist's Exposure, Health and Exposure Interventions *[Reutman]*	To research optimal ventilation and workplace risk reduction practices, and to collect pilot data on ambient mixture exposure levels, biomarkers of internal dose, and health measures to preliminarily characterize the exposures and health of nail technicians. Expected outputs include: (1) feedback provided to manufacturers of vented table evaluated by NIOSH on ventilation efficiency, ways to enhance it (if indicated) and other table features important for nail salon settings; (2) pilot data collected and analyzed to inform the design of a possible future intervention study in nail salons; (3) educational workplace exposure/risk reduction materials developed based on outputs 1 and/or 2, with distribution to nail technician audiences.
Agriculture Health Study, Pesticide Exposure Among Farmer Applicators and Their Families *[Hines]*	To conduct pesticide exposure assessment research among farmers who are participating in the Agricultural Health Study, a collaborative research effort by NCI, NIEHS, and EPA to investigate health risks among the farming population. The project will focus on characterizing the exposure of farmer applicators to selected pesticides (fungicides) and evaluating determinants of exposure.
Environmental and Take-Home Pesticide Exposures – Farm Families *[Curwin]*	To evaluate pesticide exposures among workers and special populations exposed to pesticides, including farm children, farmers, and agricultural workers handling treated commodities. The project will involve field studies to ascertain the extent to which these populations are exposed to pesticides. A combination of environmental and biological sampling will be employed. Questionnaires will be administered along with observations to determine practices and behaviors that may contribute to exposure.
Bromopropanes: Exposure Assessment of General Industry *[Hanley]*	To characterize occupational exposures to 1-bromopropate throughout industry. The study consists of plant surveys, company records, audits, industrial hygiene assessments and biomarker measurement feasibility evaluations using air sampling, exhaled breath monitoring, and urinary metabolites. Nine surveys were conducted in this study encompassing a variety of industries to comprehensively evaluate 1-bromopropane use in industry and to collect data with a spectrum of exposure levels.
Phthalates Exposure Screening and Cohort Identification *[Hines]*	To measure phthalate exposures among workers in a variety of industries in order to identify populations for possible epidemiologic reproductive health research. Information from this project will also be used in a NIOSH study of birth defects and parental exposures. Three phthalates, Di(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), and diethyl phthalate (DEP), were selected for exposure monitoring based on toxicity, use, and National Health and Nutrition Examination Survey (NHANES) urine levels. The exposure of approximately 150 workers was measured during a 3-year period using a biological monitoring method for specific phthalate metabolites.
A Case-Control Study of Primary Intracranial Gliomas Among Rural Residents *[Ruder]*	To assess the increase in brain cancer and its etiology among farmers, one occupational group in which excess risk for brain cancer has been noted. Using a case-control design, this study is evaluating associations between rural exposures and primary intra-cranial gliomas, the most common type of brain tumors, among male and female rural residents in four upper Midwestern states. It focuses on determining whether pesticides, N-nitroso compounds, electromagnetic fields, biological agents, and solvents are associated with increased glioma risk.

NIOSH/NTP Project [Project Officer]	Objective and Project Summary
Flight Crew Studies *[Grajewski]*	To evaluate the health effects of work as a flight crew member. Workplace exposures, which may potentially contribute to adverse health outcomes, include cosmic ionizing radiation and alterations of circadian rhythm. Several studies are underway to examine the risk of adverse reproductive health outcomes, cancer, and mortality.
Improved Environmental Exposure Sampling for Bioterriorism Research *[Estill]*	To expand the capacity to employ environmental sampling methods in bioterrorism emergency response investigations. Surface sampling (i.e., wipe, swab, and vacuum) and air sampling for bioterrorism agents will be evaluated. These comparisons will be completed using surrogate agents in chamber-based studies in cooperation with established bioterroristm research facilities.
Exposures and Engineering Controls in the Flavoring Industry *[Taylor-McKernan]*	To conduct a complete exposure assessment and evaluate potential engineering controls within the flavoring industry. Although a dose-response curve for various flavoring compounds and associated health effects has not been established, an engineering, solution-based approach can minimize occupational exposures.
Titanium Dioxide (TiO_2) Nanoparticle Exposure Study *[Curwin]*	To collect occupational exposure information for workers exposed to ultrafine and fine TiO_2. The data will be used by the Education and Information Division to provide information for the Current Intelligence Bulletin on TiO_2. The study objectives are: (1) to develop a strategy to measure exposure to ultrafine particles; (2) to characterize exposure to ultrafine and fine TiO_2 for various jobs and tasks at various facilities manufacturing and using TiO_2; and (3) to evaluate a strategy for measuring workplace exposure to fine and ultrafine TiO_2.
Tungsten Exposure Study *[McKernan]*	To determine if airborne tungsten oxide (WOX) fiber concentrations and physicochemical properties vary with production and manufacturing processes in the tungsten industry, and other down-stream industries that consume and incorporate tungsten in their products. The research will identify groups at elevated risk of exposure, document exposure patterns among occupational cohorts, and characterize airborne particle morphology in domestic tungsten production and use.
Inhalation Facility for Animal Exposures *[Chen]*	To provide the resources for the HELD Inhalation Facility. Inhalation exposures are conducted to simulate and mimic workplace respiratory environmental conditions. The effects of inhalation exposures on laboratory animals are analyzed by NIOSH scientists in a research program investigating the causes and mechanism(s) of respiratory occupational diseases.
Identification of Occupational Allergens *[Beezhold]*	To address concerns regarding exposures to substances that can cause inflammatory or immune reactions through the development of improved techniques for the detection of such immune reactions before adverse clinical outcomes occur through the development of improved techniques for the detection and identification of inciting occupational agents. The project will involve the analyses of clinical samples, environmental bulk samples, and environmental aerosol samples.
Reproductive Toxicity of Occupational Chemicals *[Murono]*	To evaluate how methoxychlor inhibits testosterone production by rat testicular Leydig cells. In addition, the effects of methoxychlor on estrogen formation by rat ovarian follicle cells and progesterone production by the corpus luteum will be studied. This project will elucidate the mechanism(s) of action of the pesticide methoxychlor. This mechanistic information should assist in hazard identification of selected chemicals used in the agricultural and manufacturing setting and be useful in control banding efforts.
Silica Carcinogenicity: Use of Susceptible Mouse Models *[Vallyathan]*	To investigate the magnitude of silica-induced DNA damage, apoptosis, gene changes, and oxidative stress associated with carcinogenesis. Major histopathological changes associated with silica exposure were evaluated.

NIOSH/NTP Project [Project Officer]	Objective and Project Summary
Pulmonary Toxicity of Diesel Exhaust Particles *[Ma]*	To further investigate the relationship of diesel exhaust particles (DEP) to cancer and other respiratory diseases. Exposure to DEP has been shown to induce lung cancer and enhance the development of other respiratory diseases. Recent studies showed that the mixed exposure, carbon particulate plus organic components, may induce lung toxicity through generation of intracellular reactive oxygen species (ROS).
Signaling Pathways Associated with Toxicant-induced Gliosis *[O'Callaghan]*	To characterize molecular changes associated with gliosis, a sensitive cellular index of neurotoxicity. The time-course and sensitivity of the observed responses to known and suspected neurotoxic chemicals (metals, organometals, substituted pyridines, substituted amphetamines, organic solvents) will be compared to the dosages/concentrations of neurotoxic agents required to engender gliosis.
Occupational Asthma: Inflammation and Workplace Diseases *[Luster]*	To understand the cellular and genetic events that are involved in isocyanate-induced occupational asthma and the role allergic rhinitis plays. This will allow for the development of novel intervention and therapeutic strategies and help improve the accuracy of risk assessment by providing more accurate safe exposure levels. In the genetic studies, NIOSH scientists have also shown that cytokine polymorphisms have a major influence on severity of silicosis development, Alzheimer's disease, and idipopathic pulmonary fibrosis. Studies on-going include the role of genetics in allergic contact dermatitis in healthcare workers, in musculoskeletal diseases in auto workers, in occupational asthma, and in loss of lung function in firefighters.
Trimilletic Anhydride-Induced Late-Phase Airway Responses *[Siegel]*	To evaluate pharmacologically the similarity of the present model of late airway response to that of human trimilletic anhydride (TMA) induced-asthma. TMA is a known cause of occupational asthma. It is commonly used in the production of resins and plasticizers. An experimental model of TMA-asthma has been developed. Lung function is measured, non-invasively, following a short inhalation exposure to TMA aerosol. The contribution of inflammatory cells, antibodies, cytokines, and specific allergic mediators on the asthma-like responses seen in this model will be studied.
Airway Epithelium: Target of Inhaled Toxicants *[Fedan]*	To define the role the airway epithelium plays in controlling airway reactivity. The epithelium is the initial target of the effects of inhaled toxicants. This project will examine the epithelial pathways involved in the control of airway reactivity and how they may be changed by workplace toxicants. Main outputs will be presentation and publication of basic epithelial biology findings.
Mineral Dust-induced Gene (MDIG) and Occupational Lung Diseases *[Chen]*	To understand how the MDIG is regulated upon exposure to inhaled particles and the role of induction of MDIG in pulmonary disease. The hypothesis is that induction of the MDIG is critically involved in silica-induced fibrosis and/or cancer. This project will employ molecular biology techniques to enhance our understanding of occupational lung diseases by defining the transcriptional regulation and function of this novel gene.
Mechanisms of Carcinogenesis Caused by Occupational Exposure to Metals *[Shi]*	To elucidate molecular mechanisms leading to metal-induced cancer. Specifically, the role of ROS and discrete signaling pathways in the regulation of apoptosis or cell proliferation will be determined. This project will investigate the mechanisms by which workers, occupationally exposed to metals or metal-containing particles, develop cancer.
Molecular Mechanisms of Cadmium (Cd) Carcinogenesis *[Joseph]*	To investigate the mechanisms of Cd carcinogenesis using appropriate experimental models. The expression profile of genes responsible for Cd carcinogenesis and the associated pathways and networks will be studied in cells and in experimental animals exposed to Cd. The data obtained from these studies will be used to develop biomarkers for exposure to Cd and the resulting carcinogenesis as well as to develop preventive strategies against Cd carcinogenesis.

NIOSH/NTP Project [Project Officers]	Objective and Project Summary
Exposure Assessment by Exhaled Breath/ Physiological Sampling *[Harper]*	To accurately determine worker exposure in a noninvasive way using newly developed physiologic pumps that alter their sampling rate in accordance with the worker's breathing rate to provide a more accurate measurement. Exposure measurements will be collected by using traditional pump and physiological pump sampling, and compared with direct readings from a real-time instrument. The results of this project can be used to develop a new workplace exposure assessment method and strategy.
Computational Studies of Mineral Dust Properties *[Snyder]*	To establish the molecular specificity of mineral dusts interactions with biomaterials of the pulmonary airways by studying adsorption of a pulmonary surfactant molecule on crystalline surfaces of silica quartz and kaolinite (aluminosilicate). Selective removal of this protective coating from mineral particles causes restoration of the cytotoxicity of respirable silica dusts. Using computational methods to model these interactions, NIOSH hopes to help explain why quartz silica causes silicosis while aluminosilicate (kaolinite) does not. This fundamental knowledge will advance an understanding of the properties of crystalline silica that contribute to its pathogenicity.
Systematic Microvascular Dysfunction Effects of Ultra Fine Particles vs. Fine Particles *[Castranova]*	To define the possible adverse health and environmental impact of exposure to nanomaterials and determine if pulmonary exposure to nanoparticles causes cardiovascular dysfunction. Data will be disseminated by presentation at scientific meetings, publications in journals, summaries in the NIOSH e-News and Nanotech Web page, and meetings with partners.
Evaluation of the Pulmonary Deposition and Translocation of Nanomaterials *[Mercer]*	To identify where in the lungs inhaled nanomaterials might deposit, the health risks that might arise from nanomaterial deposition, and to what extent the nanomaterials might translocate to other organs of the body after depositing in the lungs. Results of this study will address critical issues identified by the NIOSH Nanotechnology Research Center and assist in hazard identification and risk assessment.
Dermal Effects of Nanoparticles *[Shvedova]*	To assess whether nanoparticles could cause adverse effects to skin. The hypothesis is that nanoparticles are toxic to the skin and the toxicity is dependent on their penetration to skin, induction of oxidative stress, and content of transition metals. Results obtained from these studies provide critical knowledge about mechanisms of dermal toxicity of nanoscale materials and will be used by regulatory agencies (OSHA and EPA) and industry to address strategies for assurance of healthy work practices and safe environments.
Effect of Stainless Steel Welding Fume Particulate on Lung Immunity in Mice *[Anderson]*	To evaluate the effect of occupational exposure to manual metal arc-stainless steel welding fumes on the immune system. Based on previous research and preliminary data, we propose that chronic welding fume exposure is immunosuppressive resulting in decreased antibody production. This project proposes to examine the antibody response after stainless steel welding fume exposure. After an alteration in antibody production can be confirmed, a potential mechanism of action by which the welding fumes are affecting the immune system will be determined through the analysis of cellular populations and cytokine levels.
Development of New Immunodiagnostic and Detection Techniques for Indoor Fungi *[Green]*	To attempt to address the problems associated with measuring personal exposure to *Paecilomyces variotii* in occupational settings by identifying the major allergens and produce species-specific monoclonal antibodies towards these allergens. These diagnostic reagents will then be utilized to create practical immunoassays for the detection of this fungus in clinical and environmental samples.

NIOSH/NTP Project [Project Officers]	Objective and Project Summary
Development of Monoclonal Antibody-based Immunodiagnostics for Fungal Hemolysins and Potential Biomarkers *[Schmechel]*	To develop accurate and precise monitoring techniques for fungal exposure, NIOSH will produce monoclonal antibodies against five fungal hemolysins as biomarkers of exposure and develop immunoassays for their quantification in environmental and serological samples. The resulting immunoassays will provide a standardized approach for the characterization of adverse health effects associated with fungal aerosols and ultimately contribute to better patient management.
Application of QSAR and QSPR Models in Skin Sensitization Studies *[Fedorowicz]*	To develop an internet based skin sensitization predictor that can be applied to hazard identification. This will provide quick, low cost initial evaluations of a broad series of chemicals found in workplace environments. Subsequently, only chemicals with predicted skin sensitization activity would require experimental testing, thus minimizing the cost and significantly shortening the hazard identification process. The ultimate outcome of this project will be the development of an internet-based predictive tool for assessing skin sensitization potential for chemicals of interest.
The Transient Dermal Exposure: Model and Experiments *[Frasch]*	To enhance knowledge and understanding of the dermal penetration of industrial chemicals following the types of exposure that occur in the occupational setting. *In vitro* skin penetration experiments will provide data that can be compared with the predictions of computer models. This comparison permits refinement of the computer models to enhance their predictive value. A final product of this research will be a user friendly, interactive, web-based calculator that will serve as a tool for the user to estimate the amount of chemical that penetrates the skin resulting from workplace exposures.
Indoor Environment Nitrate Radical Chemistry *[Ham]*	To develop methods for the sampling and analysis of indoor reaction products, and to use these methods to determine the potential for exposure in workplaces and homes.
Indoor Chemistry of Consumer Product Mixtures *[Wells]*	To investigate the indoor reactant/consumer product reactions to more clearly define indoor workplace exposure, provide insight into important chemical structure(s) that influence indoor air quality, and highlight potential analytical/sampling needs. The research direction will be influenced by indoor environment research such as indoor pollutant characterization and measurement. The research results will yield more accurate exposure assessment, better analytical tools for Health Hazard Evaluation sampling, and improved engineering control methods to reduce chemical contaminants.
Determination of Diameter Distribution for Carbon Nanotubes (CNTs) by Raman Spectroscopy *[Chirila]*	To use Raman spectroscopy for evaluating the diameter distribution of the carbon nanotubes. By recording spectra using different laser lines, a broad diameter distribution can be determined. The process of dispersion of carbon nanotubes can be used to obtain and to measure isolated CNT and to calculate a relative number of isolated versus bundled CNTs. The results from these studies will allow NIOSH to understand the possible state of agglomeration of the CNT if they are inhaled and come in contact with pulmonary surfactant.
Dermal Penetration of Metal Working Fluid (MWF) Components *[Frasch]*	To obtain data on the permeation through skin of selected MWFs, using hairless guinea pig skin as a surrogate for human. MWF components will be selected for study based on known or suspected potential for adverse dermal effects, including irritant and allergic dermatitis and toxicity to the body. Dermal absorption rates will be compared between new, unused fluid and used fluid obtained from an industrial machining operation.

NIOSH/NTP Project/ *Project Officers*	Objective and Project Summary
Particle Size Distributions and Lead Content in Aerosol Exposures from Metal Processing Facilities *[Chisholm]*	To asses the standard closed-face cassette total dust personal sampler as a biologically relevant sampler of lead-containing aerosols in typical occupational exposures. To achieve this goal, it is necessary to accomplish two specific aims: (1) develop a method to relate measurement of a particle's projected area in a scanning electron microscope image to its aerodynamic equivalent diameter, and (2) determine the masses and particle size distributions of the filter catches and wall deposits of closed-face cassette and Institute of Occupational Medicine samplers for both laboratory and field samples of lead-containing particles.
Surface Silanol Detection in Silicon-containing Materials *[Murray]*	To determine concentrations of silanol types for respirable crystalline and amorphous mineral silicon-containing materials with known toxic behaviors to evaluate spectroscopic methods for predicting exposure risk.
Neurotoxicity After Pulmonary Exposure to Welding Fumes *[Antonini]*	To assess the pulmonary and neurotoxic effects of animals exposed by inhalation to welding fumes that are composed of varying concentrations of manganese. Results will provide mechanistic information concerning welding fume exposure and be useful for risk assessment and the development of prevention strategies to protect exposed workers.
Pulmonary Toxicity of Metal Oxide Nanospheres and Nanowires *[Porter]*	To provide fundamental toxicological data on the exposure hazard posed by TiO_2 nanospheres and nanowires. Data obtained will: (1) increase our understanding of how TiO_2 nanoparticle shape affects toxicological responses; (2) determine critical physico-chemical factors that could be exploited to reduce nanoparticle toxicity; and (3) provide a basis for initial hazard identification. In addition, these data could contribute to risk assessment studies which may ultimately establish exposure standards and recommended handling practices to avert significant human health risks in the future.
Welding Fume Metals Exposure Matrix Determination *[Keane]*	To develop enhanced exposure assessment approaches for welding fumes by detailed speciation of manganese and chromium forms in the fumes and investigation of the biologically available metals in simulated biological fluids. This approach will be applied to a spectrum of welding processes including gas metal arc steel and stainless steel, manual arc stainless steel, and altered stainless steel processes using alternate shield gases of higher and lower oxygen content to estimate the effect on toxic entities such as hexavalent chromium and oxidized manganese species. Metal ion content in simulated plasma, lysosomal fluid, and simulated pulmonary surfactant will be measured. Outputs will include peer-reviewed publications, presentations, close collaboration with ongoing toxicology studies already in progress, and communications with welding equipment manufacturers.

NCTR/NTP

NCTR/NTP

The National Center for Toxicological Research (NCTR), FDA's research center, plays a critical role in the FDA's mission. NCTR, in partnership with researchers from elsewhere in FDA, other government agencies, academia, and industry — provides innovative technology, methods development, vital scientific training, and technical expertise. The unique scientific expertise of NCTR is critical in supporting FDA product centers and their regulatory roles. NCTR conducts an array of studies that reflect the NTP mission statement. These studies, funded by NCTR voluntary allocations, are included in Table 4.

Table 4: NCTR/NTP Projects in FY 2008*

NCTR/NTP [Project Officer]	Objective and Project Summary
Effects of Caloric Restriction on Rat Testicular Tumor Formation – Collection and Analysis of Additional Tissues *[Leakey]*	To understand the role of dietary components (i.e., caloric restriction) in influencing the ultimate susceptibility of the male reproductive tract to chemical insult.
Caloric Restriction and Gene Expression in Agouti Mice *[Beland]*	To learn how calories modify the development of cancer in mice and the mechanism underlying cancer development in humans.
The Evaluation of Selected Benzodiazepine and Antihistamine Drugs in the Neonatal Mouse Tumorigenicity Bioassay and in Transgenic Human Lymphoblastoid Cells *[Fu]*	(1) To determine if the neonatal mouse bioassay can be employed to evaluate the tumorigenic potential of therapeutic drugs; (2) to examine concurrently as positive controls the genotoxic carcinogens: 4-aminobiphenyl, benzo(a) pyrene, 6-nitrochrysene, and aflatoxin B1; (3) to study the metabolism and DNA-adduct formation of benzodiazepine and antihistamine drugs by mouse and human liver microsomes to determine which, if any, cytochrome P450 (CYP) is responsible for metabolic activation in mice and humans; and (4) to study the mutations and DNA binding of the subject drugs using transgenic human lymphoblastoid cell lines expressing appropriate CYP isozymes.

**Funded by NCTR voluntary allocations*

NCTR/NTP [Project Officer]	Objective and Project Summary
A Case-Control Study of Pancreatic Cancer and Aromatic Amines *[Kadlubar]*	To measure the associations of aromatic amine exposure and metabolism with the risk of pancreatic cancer. The sources of aromatic and heterocyclic amines to be studied are cigarette smoking and diet; the metabolic capabilities to be studied are acetylator status and N-oxidation status.
Role of Acetylation and N-Oxidation in Colorectal Cancer *[Kadlubar]*	To confirm the initial findings of a pilot study regarding the roles of heterocyclic amine metabolism and exposure as putative risk factors from the diet or the environment. The sources of heterocyclic amines to be studied are cigarette smoking, diet, and cooking methods; the metabolic pathways to be studied include heterocyclic amine N-oxidation status and O-acetylation status.
Chemical Carcinogenesis: Epithelial Cells in Breast Milk *[Kadlubar]*	(1) To develop and refine a methodology for separation of luminal epithelial cells from human breast milk for DNA extraction; (2) to detect and quantify aromatic/hydrophobic-DNA adducts in luminal epithelial cells derived from human breast milk; (3) to detect genetic polymorphisms in carcinogen-metabolizing genes derived from DNA extracted from epithelial cells in human breast milk; and (4) to evaluate the relationships between carcinogen-DNA adducts and smoking status and adduct levels with polymorphisms in N-acetyltrasferase (NAT)1, NAT2, CYP1A1, and glutathione-S-transferase (GST) M1.
DNA Adducts of Tamoxifen *[Beland]*	The nonsteroidal antiestrogen tamoxifen, which is currently being used in clinical trials as a chemoprotective agent against breast cancer, has been associated with the induction of certain malignancies. To determine if tamoxifen is acting through a genotoxic mechanism, this project will characterize DNA adducts from suspected tamoxifen metabolites and develop methods for their detection and quantitation.
Novel Recruitment Techniques for a Study of Culture-Specific Diet, Metabolic Variability and Breast Cancer in African-American Women *[Ning]*	To examine the role of interindividual variability in response to exogenous agents as it may relate to breast cancer risk in African-American women. By evaluating risk associated with exposure to oral contraceptives, hormone replacement therapy, and modification of that risk by genetic variability in their metabolism, the effects of substances regulated by the FDA on breast cancer risk in African-American women may be further elucidated. Additionally, a successful model to increase African-American participation in research studies would greatly assist in future studies related to FDA-regulated substances in African-American populations.
The Role of Glutathione S-transferase genetic Polymorphisms in Breast Cancer Sensitivity to Radio- and Chemotherapy *[Ratnasinghe, Kadlubar]*	(1) To determine expression of enzymes (phenotype) in tumor tissue from women who received adjuvant therapy for breast cancer using biopsy or surgical tissue specimens, and immunohistochemistry, and to evaluate associations between phenotypes in tumor tissue and risk of breast cancer recurrence; (2) to determine inherited GSTM1, GSTT1 and GSTP1 genotypes in normal tissue from these same women, and to determine associations of GSTM1, GSTT1 and GSTP1 genotype with phenotype in tumor tissue; (3) to evaluate if GST genotypes predict breast cancer recurrence following treatment, controlling for other factors that may relate to prognosis.
The Effects of Nicotine and Other Cigarette Components on Normal and Neoplastic Human Pancreatic Cells: The Role of Low Zinc Levels on Ras, mdr-1 Genes Activation, and Metabolizing Enzyme Activities as a Possible Risk Factor for Pancreatic Cancer *[Lyn-Cook]*	(1) To determine the effects of nicotine and other cigarette components on exocrine and endocrine human pancreatic cells *in vitro* and (2) to examine ras, mdr-1, CYP1A1, and CYP1A2 expression in normal and neoplastic human pancreatic tissue grouped according to race and sex obtained from a human tissue bank.

NCTR/NTP [Project Officer]	Objective and Project Summary
Prostate Cancer: Exposure, Susceptibility and DNA Adducts *[Ning]*	(1) To determine levels of carcinogen exposure in African Americans and Caucasians with histologically confirmed prostate cancer using a case-control design; (2) to evaluate variability in hormone metabolism and susceptibility to carcinogen exposure, as measured by phenotypic and genotypic variability in carcinogen metabolism, and evaluate the interaction of these factors with the exposure data obtained in specific aim 1; and (3) to characterize DNA adducts in prostate tissue from men with prostate cancer to identify mutagenic agents and evaluate levels of adducts in relation to carcinogen exposure data and susceptibility factors obtained in specific aims 1 and 2.
In Vivo Modeling of Steroid-mediated Gender Effects in Drug Metabolism *[Kadlubar]*	(1) To characterize the activity of CYP1A2 in female subjects with regard to age, race, phase of the menstrual cycle, pregnancy, oral contraceptive usage, menopause, and homone replacement therapy (HRT); (2) to characterize the activity of CYP1A2 in male subjects with regard to age; (3) to measure estradiol, progesterone, testosterone, cortisol, interleukin (IL)-1, IL-6, and IL-10 levels in female and male subjects studied for CYP1A2 activity; (4) to correlate the activity of CYP1A2 with circulating levels of cytokines and/or circulating levels of steroid hormones; and (5) to statistically assess the impact of each of the measured variables on the CYP1A2 phenotype.
Purification of Ceramide Synthase *[Howard]*	(1) To isolate rat ceramide synthase; (2) to identify the gene coding for rat ceramide synthase; (3) to develop antibodies to rat ceramide synthase; and (4) to use the antibodies to study tissue-specific expression of ceramide synthase.
Photoinduction of Cutaneous Malignant Melanoma in TP-ras/ink4A (+/-) Transgenic Mice *[Tolleson]*	(1) To characterize photochemical DNA damage in the skin of TP-ras/ink-4a mice exposed to UVA+UVB radiation; (2) to determine whether cutaneous malignant melanoma can be induced in neonatal TP-ras (+) ink4a (+/-) transgenic mice using UVA+UVB radiation; (3) to identify photochemically induced mutations within the ink4a/p16/CDKN2A and p53 loci in tumor tissues; and (4) to determine whether UVA+UVB exposure at an early age creates a greater risk for developing cutaneous melanoma in TP-ras (+) ink4a(+/-) mice compared with chronic ultraviolet (UV) A+UVB exposure of older animals.
Mechanisms and Consequences of DNA Damage and Methylation Dysregulation During Rat Hepatocarcinogenesis *[Pogribny]*	(1) To confirm that the presence of uracil and abasic sites in preneoplastic DNA from folate/methyl deficient rats creates nonproductive high-affinity binding sites for the DNA methyltransferase that compromise normal DNA methylation at the replication fork resulting in genome-wide hypomethylation; (2) to determine: whether the double-stranded loss of cytosine methylation is maintained in folate/methyl-deficient rats after nutritional repletion of methyl donors or whether the original methylation pattern and chromatin structure can be reestablished or whether the increase in expression is stimulated by global loss of methyl groups and whether DNMT1 expression is decreased by methyl repletion; (3) to determine the temporal relationship between the appearance of DNA lesions and site-specific methylation within the CpG (cytosine-phosphate-guanine) island of the p16 promoter region in p16 gene expression with alterations in local chromatin structure and DNA methyltransferase mRNA levels and activity; and (4) to use microarray slides printed with the rat cDNA library as a tool to screen for methylation-related down-regulation of candidate genes in hepatic preneoplastic foci, preneoplastic nodules, and tumor tissue from folate/methyl-deficient rats.
Effect of p53 Genotype on Gene Expression Profiles in Mice Exposed to the Model Mutagen, N-ethyl-N'-nitrosourea (ENU) *[Morris]*	(1) To determine the effect of mutation in the p53 tumor-suppressor gene on gene-expression profiles in young and aged mice and (2) to determine the effect of mutation in p53 tumor-suppressor gene on gene-expression profiles in young and aged mice exposed to the model mutagen, N-ethyl-N-nitrosourea.

NCTR/NTP [Project Officer]	Objective and Project Summary
Mechanism of Biotin Deficiency-induced Malformations *[Hansen]*	(1) To determine if palatal tissue from biotin-deficient embryos is able to fuse *in vitro* in either biotin-sufficient or -deficient medium; (2) to determine if arachidonic acid increases palatal fusion and improved limb development and increases the length of the long bones *in vitro* from biotin-deficient mouse embryos; (3) to determine if prostaglandin E2 increases palatal fusion and improved limb development and increases the length of the long bones *in vitro* from biotin-deficient mouse embryos; (4) to determine if malonyl CoA increases palatal fusion and improves limb development and increases the length of the long bones *in vitro* from biotin- deficient mouse embryos; (5) to determine fetal arachidonic acid content and synthesis *in vivo*; and (6) to determine if arachidonic acid is able to prevent biotin deficiency-induced orofacial clefting and limb hypoplasia *in vivo*.
Determining the Neurotoxic Profile – Specific Changes in Cortical Gene Expression Resulting from Amphetamine Exposures: Laser Capture Microdissection- and cDNA Array-Assisted Research *[Bowyer]*	(1) To determine the importance of the innervation of the dopaminergic and glutamatergic neurotransmitter systems in the neurodegeneration produced in the interneurons in parietal cortex layers II and IV using specific antagonists and agonists of these two systems; (2) to determine the gene-expression pattern changes that occur in parietal cortex layers II and IV when amphetamine-induced neurodegeneration is produced under normothermic, 2-day amphetamine exposure, conditions using cryostat-assisted dissection; (3) to analyze the changes in gene expression in parietal cortex layers II and IV in the same manner as in Objective 2, but in animals that are given an acute neurotoxic exposure to amphetamine and become extremely hyperthermic; (4) to determine, using cryostat-assisted dissection, the changes in gene expression that occur in layer III of the parietal cortex under conditions that do not produce neurodegeneration, and compare this expression pattern to that produced from an acute amphetamine exposure where severe hyperthermia occurs and extensive degeneration occurs in pyramidal cells of layer III; and (5) to determine, using laser capture microdissection, whether astrocytes and microglia respond differentially to the two dosing paradigms in the absence or presence of neurodegeneration.
Methods for Support of a Functional Proteomics Facility at NCTR *[Yu]*	(1) To establish and standardize for routine-use procedures for whole cell and subcellular organellar isolation for a variety of tissues; (2) to develop and standardize specific and sensitive markers of cell type and organellar purity and yield; (3) to identify, adapt, develop, and standardize appropriate 2-D protein separation techniques; and (4) to integrate results of specific aims 1-3 to provide “front-end” components of a functional proteomics facility.
Transgenic Mouse Model for Detecting *In Vivo* Mutation Using a Green Fluorescent Protein Reporter *[Dobrovolsky]*	(1) To produce two lines of transgenic mice expressing the tetracycline-repressor protein; (2) to investigate the efficiency of *in vivo* repression of green fluorescent protein in various tissues of different lines of the double-transgenic mice; and (3) to determine the frequency of spontaneous and y-ray-induced tetracycline-repressor protein mutation in lymphocytes of double-transgenic mice using flow cytometry.
Analyses of the Rat Hippocampus via DNA Microarrays and a Novel Antibody Array, Coupled with Laser Capture Microdissection– Evaluation of the Effect of Aging on Gene and Protein Expression Associated with Learning *[Patterson]*	(1) To measure gene and protein expression in regions of the hippocampus to determine regional distribution; (2) to determine the effect of aging on regional distribution of hippocampal proteins in three strains of rats; (3) to determine if aging, behavioral performance, and alterations in gene and protein expression in the hippocampus are related; and (4) to correlate the differences in gene and protein expression with behavioral performance of young adult and aged rats in a learning task previously shown to be sensitive to changes in protein expression.
An Efficient Regulatory Method for Evaluating Chromosomal Damage: Analysis of Micronucleus in Different Rat Strains by Flow Cytometry *[Aidoo]*	Provide the information necessary to establish a new standard for pre-market cytometric scoring of micronuclei in Sprague-Dawley and Fischer 344 rats; evaluation of genotoxic potential by: (1) establishing the validity of the flow (2) determining the kinetics of the appearance and elimination of micronucleated cells in both strains; and (3) determining whether the frequency of micronuclei in the young circulating reticulocytes accurately reflects the frequency in the primary bone marrow cell population from which they are derived.

NCTR/NTP [Project Officer]	Objective and Project Summary
Sulfotransferase 1A1 (SULT1A1) Genotype and Phenotype in Relation to Efficacy of Tamoxifen Treatment *[Ning]*	(1) To determine whether induction of SULT1A by 4-hydroxy-tamoxifen results in an increase in expressed protein and enzymatic activity toward environmental estrogens in tamoxifen-treated breast-cancer patients; (2) to determine the effect of 4-hydroxy-tamoxifen on SULT1A1 activity in breast-cancer cell lines; (3) to determine SULT1A1 genotype in tamoxifen-treated women and genotype-phenotype correlations; and (4) to archive blood samples, administer the Block 98 Questionnaire, and determine the survival data for future studies.
Assessment of Depression Risk Associated with Accutane (13-cis-Retinoic Acid or Isotretinoin) and All-Trans-Retinoic Acid Treatment: Measurement of Behavioral and Neurochemical Alterations in Adult Sprague-Dawley and Flinders Sensitive and Insensitive Line Rats *[Ferguson]*	(1) To establish the necessary oral doses of 13-cis-retinoic acid and all-trans-retinoic acid in rats that produce peak plasma levels similar to those of humans prescribed 13-cis-retinoic acid; (2) to measure the toxicity and pathology associated with long-term oral treatment with 13-cis-retinoic acid and all-transretinoic acid in rats; (3) to describe the behavioral alterations associated with chronic 13-cis-retinoic acid and all-trans-retinoic acid treatment in adult male and female Sprague-Dawley rats; (4) to determine if such alterations resemble those described in humans treated with 13cis-retinoic; (5) to measure sex differences in behavioral response to 13-cis-retinoic acid and all-transretinoic acid treatment; (6) to evaluate the reversibility of the 13-cisretinoic acid induced and/or all-transretinoic acid-induced alterations; (7) to assess if genetic predisposition to depression determines the frequency and/or magnitude of the behavioral alterations associated with 13-cis-retinoic acid and/or all-trans-retinoic acid treatment; and (8) to quantitate the neurochemical alterations induced by 13-cis-retinoic acid and/or all-trans-retinoic acid treatment.
The Development of Rapid Spectral-Based Pathogen Identification Methods for Food Defense and Counter-Bioterrorism *[Buzatu]*	To develop the necessary computational capability to enable the rapid identification of pathogen/nonpathogen microorganisms, nonbiological hoax materials, and mixtures of all mentioned collected real-world situations. An analysis will be done of the salient spectral features necessary for identifying these substances, and the effect of both instrumental and pattern definition techniques on the ability to use these features for rapid identification.
Rapid Bacterial Identification with Subspecies-Level Specificity *[Wilkes]*	To develop a complete instrumental/ computational system for rapid bacterial identification at the subspecies level and demonstrate its utility in simulated counterterror and food defense.
Development of a Microarray Chip for the Detection of Multiple Antibiotic Resistance Markers *[Khan]*	To develop a microarray-based method for the detection of 150 genes associated with 22 antibiotics, some of which are used to promote growth in poultry and animal farming while others are used to treat infections in both humans and animals. The data generated by the use of the chip in monitoring and tracking the spread of resistance markers may be helpful for the FDA in making regulatory decisions that require banning and/or approving the use of certain antibiotics in poultry and farm animals.
Analytical Methodology Development for Assessing Bioactive Herbal Ingredients in Functional Foods *[Heinze]*	To develop qualitative and quantitative methods for determination of specific marker compounds such as terpene trilactones (ginkgolides and biolobalide) and kava lactones in raw plant materials, dietary supplements, and functional food products containing ginkgo, kava kava, or their extracts. A minor objective of this proposed work is to include other minor compounds which do not meet the selection criteria but may be of safety concerns. These compounds include ginkgolic acids, ginkotoxin, and urushiols in gingko products and unknown factors in kava.
Effect of Soy-Containing Diets on Ammonium Perchlorate-Induced Thyroid Toxicity in Sprague-Dawley Rats *[Doerge]*	To determine the effect of dietary soy and genistein, the principal soy isoflavone, on the dose-response characteristics for perchlorate-induced thyroid toxicity in male Sprague-Dawley rats.

NCTR/NTP [Project Officer]	Objective and Project Summary
Assessment of Interindividual Variability in Expression of DNA Methyltransferases, (DNMT) 3a, and DNMT3b, in Liver and Identification of Factors Influencing Expressions *[Hammons]*	(1) To determine levels of expression of DNMT3a and DNMT3b in liver samples from a pool of donors selected according to smoking status, gender, and age; (2) to determine the effect of tobacco smoke on DNMT1, 3a, and 3b expression in liver-cell systems; and (3) to assess the polymorphism frequency identified in DNMT3b in the sample pool included in the study and assess whether it is correlated with expression.
Estimation of Lag Time Between Onset of and Death from an Occult Tumor via Attribution of Tumor Lethality *[Moon]*	Develop new statistical methods for estimating the elapsed time between onset of and death from an occult tumor when cause of death for each animal or context of observation for each tumor is not available.
Global and Locus-specific DNA Hypomethylation: A Common Mechanism Involved in Genotoxic and Non-genotoxic Rat Hepatocarcinogenesis *[Pogribny]*	(1) To determine if the temporal alterations in genomic-methylation profile in preneoplastic liver tissue observed in the folate/methyldeficient model of rat endogenous hepatocarcinogenesis also occur in other carcinogenesis model; (2) to identify genes that are consistently up- or down-regulated in target tissue during the promotion stage of carcinogenesis; and (3) to evaluate whether or not the global and locus-specific DNA hypomethylation, along with aberrant expression of related genes and changes in chromatin conformation, is specific only to target tissues and may be used for early detection of chemicals with carcinogenic potential.
Carcinogenicity of Acrylamide and its Metabolite Glycidamide in Rodents: Neonatal Mouse Bioassay *[Beland]*	To compare the carcinogenicity of acrylamide and its metabolite glycidamide in B6C3F1 mice treated neonatally.
Biomarkers of Liver Disease and Toxicity *[Beger]*	To develop biomarker profiles for normal individuals and those with liver diseases or toxicity.
Assessment of Ketamine in the Developing Nonhuman Primate *[Wang]*	(1) To determine, using neurohistochemical approaches, if, and at what developmental stages, ketamine exposure increases neuronal apoptosis/proliferation; (2) to determine, using neurohistochemical approaches, the dose-response for ketamine to produce apoptosis at the most sensitive developmental stage; (3) to determine the reversibility or permanence of the response using behavioral, imaging, and neurohistochemical approaches; and (4) to determine, at the most sensitive stage and dose, genomic and proteomic responses to ketamine treatment.
The Development of Novel Nanotube-Based Technologies That Benefit Public Health, Protect the Public, Produce High-Efficiency Separations and Filtration, and Improve Energetic Material Therapeutics *[Buzatu]*	To take advantage of the unique physical and electrical properties of nanotubes to develop: (1) novel technologies for the filtration of chemical and biological hazards from air, water, blood, and other media; (2) technologies that protect public health or otherwise benefit the public; and (3) novel nanotube/monoclonal antibody-based cancer therapies.
Prioritizing Sources of Variability in Genomic Profiling Data for Standards and Guidance Development *[Fuscoe]*	To prioritize sources of variability in microarray data to determine how to focus additional experimental queries, guidance development, and experimental standards. The outcome should be an enhanced capability to address standards development and accept new technologies as they arise. To evaluate the potential benefits or detrimental effects of dietary phytoestrogens on breast-cancer progression, adipose tissue, and the brain using well-established laboratory animal models.
Development of a physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) Model for Acrylamide *[Doerge]*	(1) To develop a PBPK/PD model for acrylamide and glycidamide; (2) to determine mutagenicity of acrylamide and its metabolite glycidamide in Big Blue® rats; and (3) to determine the DNA-adduct levels and the extent of mutagenicity of furan and its metabolite cis-2-buten-4-dial in neonatal B6C3F1/Tk+/- mice.
Benefit/Risk Classification Models for Regulatory Decision Making in Personalized Medicine *[Chen]*	To develop prediction models and computational methods for quantitative assessment of benefit/risk models for regulatory decisions in personalized medicine.

NCTR/NTP [Project Officer]	Objective and Project Summary
Optimal Tree-Based Ensemble Methods for Class Prediction *[Baek]*	(1) To build on the novel Decision Forest Classification Model developed at NCTR to produce an ensemble of decision trees, each constructed from a different set of predictors, by statistically pruning to optimal size using cross-validation and (2) to use Monte Carlo simulation techniques to compare the performance of the proposed Decision Forest classifiers to the performance of a single optimal decision tree. A primary area of application is the classification of subjects into risk categories in class-prediction problems occurring with genomics and proteomics data.
Microbial Degradation of Fluoroquinolone Antimicrobial Agents *[Sutherland]*	To identify microorganisms that either completely degrade fluoroquinolones or modify the fluoroquinolone molecule so as to reduce its toxicity to bacteria.
Evaluation of the Genetic Toxicity and Behavioral Effects of Chronic Methylphenidate Exposure in Juvenile Male Rhesus Monkeys (Macaca mulatta) *[Morris]*	(1) To determine the baseline frequency of measures of genetic damage in a population of juvenile rhesus monkeys; (2) to determine the frequency of these measures of genetic damage in a population of juvenile rhesus monkeys at defined intervals during a chronic exposure to methylphenidate; (3) to determine if chronic exposure to methylphenidate results in measurable effects on the behavior of juvenile rhesus monkeys utilizing the NCTR Operant Test Battery; and (4) to determine the plasma concentration of methylphenidate and its major metabolite ritalinic acid during the chronic exposure of juvenile rhesus monkeys to the drug.
Evaluation of the Genotoxicity and Pharmacokinetics of Methylphenidate in Male Big Blue Mice *[Manjanatha]*	(1) To determine the metabolites of methylphenidate at early times after exposure in B6C3F1 mice to compare the major metabolites in the human, monkey, and mouse; (2) to determine the plasma levels of methylphenidate and its major metabolites in the B6C3F1 mouse after 28 days of exposure; (3) to determine the effect of exposure to methylphenidate on body and organ weights of the B6C3F1 mouse after 28 days of exposure; (4) to determine if long-term exposure to methylphenidate results in a dose-responsive increase in the liver c11 gene mutant frequency of Big Blue® mouse; and (5) to determine the pharmacokinetics of methylphenidate and its major metabolite ritalinic acid in B6C3Fa mice.
Biotransformation of Isoflavonoid Phytoestrogens by Colonic Microfloras *[Rafii]*	To use fecal samples of monkeys and rodents to find out if the metabolites produced by intestinal microfloras of experimental animals exposed to phytoestrogens are the same as those of humans or whether the animal colonic bacteria metabolize them to different compounds. This information is necessary for extrapolation to humans of the data obtained from treatment of animals with phytoestrogens.
Sex Differences in Chemotherapeutic Toxicity: Profiling of Transporter Genes in Human Liver *[Lyn-Cook]*	(1) To identify sex differences in the gene expression of drug transporters known to be involved in transport of chemotherapeutic drugs and with hepatic expression in human liver tissues. This is prerequisite to elucidating the mechanisms of interindividual variability in hepatic drug transport systems; (2) to evaluate sex-related hepatic drug-transport function including both of the basolateral transport systems that are responsible for translocating drugs across the sinusoidal membrane and the active canalicular transport systems that are responsible for the biliary excretion of drugs using sandwich-cultured human hepatocytes; (3) to characterize the relationships between transporter-gene expression and uptake or excretion of chemotherapeutic drugs defined with the sandwich model and transporter-transfected cell lines; (4) to evaluate the effects of sex hormones on hepatic-transporter gene expression in human cancer-cell lines and sandwich-cultured hepatocytes; (5) to identify and validate novel transporter-drug correlations using a chemogenomic approach followed by cytotoxicity and drug-uptake studies in cell lines overexpressing specific transporter genes; (6) to develop an *in silico* pharmacokinetic modeling program based on the data from sandwich-cultured hepatocytes to predict potential *in vivo* drug pharmacokinetics and toxicity in men and women; (7) to develop guidelines and recommendations for clinical-trial design and analysis of sex differences in new drug applications.

NCTR/NTP [Project Officer]	Objective and Project Summary
Molecular Mechanisms Underlying Gender-Associated Differences in the Adverse Reactions to the Anti-Retroviral Agent Zidovudine (AZT): Role of Mitochondrial Toxicity *[Desai]*	To elucidate molecular mechanisms of mitochondrial dysfunction that will address gender-based differences in adverse effects of anti-retroviral drugs such as AZT. This will provide critical information to the FDA for the development of guidelines to plan new treatment strategies to reduce the frequency and severity of antiretroviralrelated toxic effects in women, particularly in pregnant women.
Neurotoxicity Assessment of Manganese (Mn) Nanoparticles in PC 12 Cells and in Mice *[Ali]*	To evaluate the neurotoxicity (genomic changes, reactive oxygen species, lipid peroxidation, antioxidant enzymes, glutathione, neurotransmitter concentrations, morphological changes) of different sized manganese nanoparticles using PC 12 cultured cells.
Ketamine Pharmacokinetics in Children *[Doerge]*	To develop and validate a sensitive liquid chromatography/mass spectroscopy (LC/MS/MS) method to quantify the enantiomers of ketamine and nor-ketamine in plasma from children dosed with racemic ketamine during surgical procedures. These measurements will be the basis for pharmacokinetic evaluation of ketamine and nor-ketamine enantiomers in children. This laboratory investigation at the NCTR is part of an Arkansas Children's Hospital protocol to better understand the disposition of ketamine in infants and children undergoing cardiopulmonary bypass.
The Effects of Acrylamide and PhIP on Normal Human Brain Cortical Neuronal (HCN-1), PC12, and HepG2 Cells *In Vitro*: Activation or Inactivation of Phase I and II Enzymes *[Tareke]*	(1) To determine the effects of acrylamide and/or PhIP on cell proliferation, transformation, toxicity, apoptosis, and neurotransmitters turnover in HCN-1 and PC12 cells; (2) to determine the effects of acrylamide and/or PhIP on the expression of CYP 1A1, 1A2, 1B1, 3A4, and GSTs in HepG2, PC12, and HCN-1 cells; and (3) to determine whether the dietary agents I3C and sesame seed lignans modulate the effects of acrylamide and/or PhIP.
Cancer Mutations as Biomarkers of Cancer Risk: Human Studies with Implications for Personalized Medicine *[Parsons]*	(1) To develop the information necessary for the rational use of oncogene mutations as quantitative biomarkers of cancer risk; (2) to compare the information derived from human tissues with data generated in a parallel rodent protocol as an approach for incorporating carcinogenesis-relevant data into the rodent to human extrapolation necessary in cancer risk assessment; (3) to validate a streamlined allele-specific competitive blocker (ACB) polymerase chain reaction (PCR) methodology and develop the methodology necessary to measure oncogene mutant fraction in cell-free DNA isolated from plasma; and (4) to convey to the regulatory risk assessment community the regulatory significance of the data regarding tumor-associated mutations which have, and will be, generated.
Liver Toxicity Biomarkers Study: Phase 1, Entacapone and Tolcapone *[Beland]*	To establish liver-toxicity biomarkers and associated algorithms for use in preclinical drug development that will predict the probability of occurrence of hepatocellular injury at any subsequent phase of drug development or following approval of the drug for marketing. Emphasis will be placed upon drugs that do not demonstrate "classical" signs of liver toxicity during preclinical stages of drug development.
Natural History of Acute Kidney Injury at Central Arkansas Veterans Healthcare System *[Beger]*	To test clinical biomarkers of acute kidney injury identified from previous studies that precede the rise in serum creatinine and blood urea nitrogen and can be measured in easily obtained urine samples from patients. This project addresses the need for more clinical biomarkers of toxicity outlined in the Critical Path Initiative.
Evaluating the Utility of ACB-PCR in Dose-Response Assessment and Mode-of-Action Evaluation *[Parsons]*	1) To further develop, evaluate, and disseminate a new NCTR method, ACB-PCR; and 2) to determine whether ACB-PCR measurements of specific oncogenic-base substitutions can be used to inform and improve the dose-response and mode of action assessments required in cancer risk assessment.
Maintenance of Defined Flora Associated BALB/c and TG26 Mice in Isolators for Use in Future Protocols *[Wagner]*	To maintain a colony of defined-microbiota BALB/c and Tg26 mice in gnotobiotic isolators between approved protocols.

NCTR/NTP [Project Officer]	Objective and Project Summary
Mechanisms of Gender Differences in Aspirin Effects: Metabolizing Enzymes and Therapeutic Targets *[Ning]*	(1) To profile gender differences in the mRNA expression and protein production of drug-metabolizing enzymes known to be involved in aspirin metabolisms, using human liver samples from 50 males and 50 females; (2) to characterize molecular mechanisms of sex hormones (estrogens, progestogens, and androgens) in regulation of the expression of aspirin-metabolizing genes in human estrogen receptor (ER)-positive hepatic-cell line HepG2-ER(+), using biochemical procedures including DNA-protein binding assay and reporter construct assay; (3) to measure sex-hormone modulation of aspirin effect on platelet aggregation and its related biomarkers [cyclooxygenase (COX)-1, COX-2, prostaglandin (PGE)2, thromboxane A2 (TXA2), and leukotriene B4 (LTB4)] using human platelet precursor cells; (4) to identify sex-hormone modulation of aspirin actions in human endothelial and epithelial cell lines, by measuring prostacyclin dynamics (PGE2, TXA2 and LTB4) and aspirin-targeting enzymes [COXs, nitric oxide synthase (NOS), and lipoxygenase (LOX)] expression; and (5) to evaluate sex-hormonal modulation of response to aspirin in apoliprotein E-deficient mice.
Sex Differences in Drug Abuse Susceptibility in Methylphenidate (MPH)-Treated Rats *[Ferguson]*	To determine potential sex differences in substance abuse susceptibility after methylphenidate (Ritalin®) treatment during adolescence. To date, substance abuse susceptibility post-methylphenidate treatment has been determined in boys and male rodents only. If sex differences do exist, the patient information for methylphenidate can be altered such that girls with Attention Deficit Hyperactivity Disorder undergoing stimulant treatment receive differential monitoring for later substance use disorders. The hypothesis is that male and female rats that have been treated with methylphenidate will exhibit different levels of drug abuse susceptibility.
Histochemical Test Battery for Evaluating the Efficacy and Toxicity of Putative Alzheimer Disease Therapeutics of FDA Relevance *[Schmeud]*	To test the hypothesis that Alzheimer's Disease, which is characterized by the deposition of insoluble amyloid plaques in the brain, is the result of a cascade of pathological processes and that pharmacological intervention at various points within this sequence of events could attenuate the resulting pathology.
Sex Differences in Systemic Lupus Erythematosus: Effects of a Single Nucleotide Polymorphism in the Prolactin Gene on Individual Response to Prasterone Therapy [Lyn-Cook]	To elucidate whether the prolactin-1149G single nucleotide polymorphism increases systemic lupus erythematosus susceptibility by modulating signal-transduction pathways in a manner reversible by prasterone.
Mechanistic Evaluation of the Induction of Lymphoproliferation and Apoptosis Inhibition by Probiotic Bacteria in Mice Infected with *Salmonella enterica* *[Wagner]*	(1) To orally challenge defined human microbiota-associated (HMA) BALB/c mice and probiotic-bacteria-treated HMA BALB/c mice with *Salmonella enterica* and isolate intestinal mucosal-associated lymphoid tissues (MALT), including: Peyer's patches, lamina propria, and mesenteric lymph nodes; (2) to use pathway-focused gene-expression profiles generated from real-time RT-PCR expression arrays to compare signal transduction in MALT from HMA mice treated with or without probiotic bacteria and orally challenged with S. enterica; (3) to develop immunohistochemical and *in situ* hybridization conditions to detect the expression of the signal pathway molecules implicated in activation and apoptosis inhibition in mucosal T-cells and accessory cells in tissue sections of Peyer's patches, lamina propria, and mesenteric lymph nodes; (4) to conduct immunohistochemical and *in situ* hybridization studies on tissue sections for detection of molecules involved in the regulation of lymphocyte activation and programmed cell-death pathways induced by bacterial surface antigens; and (5) to compare the probiotic-treated and untreated mice for expression of dendritic cell, macrophage, and intestinal epithelial cell-derived cytokines.

NCTR/NTP [Project Officer]	Objective and Project Summary
Sex Differences in Molecular Biomarkers for Individualized Treatment of Non-Gender-Specific Disease: A Novel Classification Algorithm for the Development of Genomic Signatures from High-Dimensional Data *[Chen]*	To find sex-specific high-dimensional biomarkers: (1) to develop classifiers for each sex using our Classification by Ensembles from Randon Partitions algorithm as well as several alternative algorithms; (2) to investigate the improvement in these high-dimensional biomarkers using the variable importance derived from our classification algorithm to prioritize and combine features; (3) to find optimal cutoffs to select high-dimensional biomarkers and finalize the classification algorithm; (4) to assess the performance of sex-specific high-dimensional biomarkers from our classification algorithm by cross-validation to obtain a valid measure of prediction accuracy using publicly available high-dimensional non-gender-specific data; and (5) to develop a user-friendly classification software tool that is downloadable from the Internet.
Behavioral Phenotype of the Tg.AC Mouse *[Ferguson]*	To quantify behaviors of the transgenic mouse strain Tg.AC proposed as an alternative to the traditional 2-year chronic bioassay for carcinogenesis. Behaviors of the parent, hemizygous and homozygous strains will be compared. This "behavioral phenotyping" and is routinely conducted with new transgenic mouse strains in which central nervous system alterations are suspected.
Neurotoxicity Assessment of Silver (Ag) Nanoparticles in PC-12 Cells and in Rats *[Ali]*	(1) To evaluate the neurotoxicity of different sizes of Ag-nanoparticles using cultured PC-12 cells; (2) to determine if *in vitro* exposure to Ag nanoparticles selectively induces specific genomic changes in cultured PC-12 cells using microarrays; (3) to determine if single or multiple doses of Ag-nanoparticles produce ROS, alterations in lipid peroxidation and/or changes in antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase) and glutathione levels in the rat brain; (4) to determine if single or multiple doses of Ag-nanoparticles induce specific genomic changes in the rat brain as indicated with microarrays; (5) to determine if single or multiple doses of Ag-nanoparticles produce significant changes in neurotransmitter concentrations in the brain in rat; (6) to determine if single or multiple doses of Ag-nanoparticles produce significant changes in the formation of 3-nitrotyrosine (3-NT), an *in vivo* biomarker for oxidative stress, in the rat brain; and (7) to determine if multiple doses of Ag-nanoparticles produce morphological alterations in blood-brain barrier, brain, or other visceral organs of the rat.
Assessment of Gaseous Anesthetics in the Developing Nonhuman Primate *[Wang]*	(1) To evaluate dose-response effects of gaseous anesthetics: a) to determine if prolonged exposure to nitrous oxide or isoflurane alone will result in an increase in neuronal cell death; b) to determine if combinations of nitrous oxide and isoflurane will prevent or enhance each other's effects on the developing nonhuman primate; (2) to determine if a relative high-dose or prolonged exposure of the developing nonhuman primates to nitrous oxide or isoflurane alone, or their combination will induce long-term behavioral deficits, as well as long-lasting pathological changes; (3) to determine, using noninvasive imaging techniques [High resolution dedicated positron emission tomography (microPET) and MRI], if a high-dose or prolonged exposure of the developing nonhuman primates to nitrous oxide or isoflurane alone, or in combination will induce long-lasting pathological changes; and (4) to identify potential underlying mechanisms that could link alteration of mitochondrial function and elevation of ROS to gaseous anesthetic-induced neuronal cell death. L-carnitine will be used to attenuate neurological brain injury associated with mitochondria-related degenerative effects induced by gaseous anesthetics in the developing nonhuman primate.
Evaluation of Growth and Pubertal Development in Male Rhesus Monkeys (Macaca mulatta) Chronically Exposed to Methylphenidate Hydrochloride *[Fu]*	Following examination of the genetic toxicity associated with chronic methylphenidate hydrochloride treatment, this study will continue dosing through the completion of puberty, to allow for evaluation of changes in pharmacokinetics and operant behavior testing.

NCTR/NTP [Project Officer]	Objective and Project Summary
Laboratory Studies in Melamine and Cyanuric Acid Biochemical Toxicology *[Tolleson]*	To determine chemical and biochemical properties of melamine and cyanuric acid that may influence their toxicity and retention as tissue residues.
Assessment of Effects and Metabolism of Synthetic Azo Colorants Used in Women's Cosmetics on Human Skin Microbiota *[Chen]*	To evaluate the metabolism and effect of color additives used in cosmetics on the skin microbiota with a potential to adversely affect women's health. Specific objectives are: (1) to assess the degradability of the synthetic azo colorants in cosmetics by skin bacteria; (2) to identify and quantify the potential carcinogenic and toxic aromatic amines in the metabolites; (3) to elucidate the role of the microflora with potential genotoxic effects of cosmetic azo dyes on women's health; (4) to determine physicochemical properties of the azo dye degrading enzymes from the skin bacteria; and (5) to establish a standardized assay to determine the reductive capacity of the skin microflora on the azo colorants.
Baseline Practices for Analyzing Genome-Wide Association Study Data *[Hong]*	To compare the latest methods for analyzing genome-wide association study data with a focus on developing baseline practices.
Genotyping of Transporter Genes Associated with Gender Differences and Promoter Methylation of UGT1A1 in Human Liver: A Means of Assessing Safety and Toxicity of Chemotherapeutic Drugs *[Lyn-Cook]*	(1) To identify polymorphisms in drug-transporter genes identified to be differentially expressed according to gender in human liver samples; (2) to correlate polymorphism frequencies in male and female to gene expression; (3) to evaluate the methylation profile of UGT1A1 promoter in human-liver samples from male and female and correlate it to expression of UGT and its activity; and (4) to evaluate effects of polymorphisms in transporter genes on uptake and clearance of chemotherapeutic drugs in a functional assay using the B-CLEAR human *in vitro* model.
Mechanistic study of glitazone-induced hepatotoxicity by integrating gene expression, metabolic and proteomic profiles *[Guo]*	(1) To evaluate *in vitro* hepatotoxicity of anti-diabetic glitazones (TZDs) including troglitazone, ciglitazone, rosiglitazone, and pioglitazone; (2) to identify gene expression signatures associated with effects of treatment by TZDs; (3) to measure synthesis profiles of hundreds of metabolites (nontargeted) and the turnover of specific metabolites involved in certain liver cell specific metabolic pathways (targeted and non-radiating stable isotope tracer substrate approach to label glycogen, RNA, DNA, sterol and fatty acids); (4) to measure hundreds of liver-specific proteins in cell culture media and quantify the turnover rate of certain liver-specific membrane enzymes (transminases); (5) to identify enriched genes, metabolites and proteins responsible for separating and correlating the toxicity endpoints. These endpoints include the levels of 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, adenosine triphosphate, turnover rate of various hepatic transaminases and apoptotic responses defined to measure toxic versus non-toxic responses to drug treatments); (6) to integrate the disparate data to reconstruct pathways and networks using existing computational models such as hierarchical approach or new models to be developed; and (7) to identify genes, processes and biomarkers associated with TZD-induced toxicity.
Interaction of Dietary Resveratrol with Intestinal Microflora *[Sutherland]*	(1) To identify how resveratrol, an investigational botanical drug that has already been highly publicized and sold as a dietary supplement, alters the population dynamics of the human intestinal microbiome and thus affects overall health; (2) to determine how the microorganisms affect resveratrol, making it more or less effective as a drug or bioavailable for absorption; (3) to develop a model system for bacterial interactions with dietary supplements, whereby the microbial perturbations caused by this and other dietary supplements can be monitored and the metabolism of this compound by the microbial community can be detected; and (4) to understand how the dynamics of the intestinal microbial community are altered by long-term, high-dose use of resveratrol.

NCTR/NTP [Project Officer]	Objective and Project Summary
Chemical Inactivation of Protein Toxins on Food Contact Surfaces *[Tolleson]*	(1) To identify cleaning/sanitizing treatments that result in elimination and/or inactivation of protein toxins (abrin and ricin) on food-contact surfaces; (2) to identify surrogate(s) that can be used to study chemical inactivation of abrin or ricin; and (3) to measure the loss of ricin and abrin biological and biochemical activities in the presence of cleaning/sanitizing solutions using RAW264.7 macrophage cytotoxicity assays and 28S rRNA adenosine N-glycosidase RTqPCR-based enzyme assays.
Evaluating the Effects of Over the Counter Skin Products, such as Sunscreen, on the Absorption of Dermally Applied Estradiol, in an *In Vitro* and *In Vivo* Model *[Gopee]*	(1) To investigate the pig as an animal model that will allow the measurement of systemic estradiol when it is applied dermally; (2) to use the animal model to mimic the clinically reported effects of sunscreen application on estradiol absorption from topically applied estradiol products; (3) to evaluate factors, such as components in sunscreens or time of application, on the rate and extent of estradiol absorption from dermally applied products; (4) to develop an *in vitro* system to study and determine the individual components or combination of components in sunscreens responsible for the enhancement in the absorption of estradiol from topically applied estradiol products; and (5) to use this *in vitro* model to evaluate factors that may impact absorption of estradiol from dermally applied products.
Method Development for Study of Antioxidant Properties in Dietary Supplement *[Fu]*	***Microsomal Metabolism Mediated Studies:*** (1) To determine if the studied herbal dietary supplements can enhance or inhibit free-radical formation, mediated by microsomal metabolism, in a dose dependent manner; and (2) to determine if the studied herbal dietary supplements can enhance or inhibit microsomal metabolism-mediated lipid peroxidation in a dose dependent manner. ***Cell Culture Studies:*** (1) To determine the toxic effects, including mitochondrial dehydrogenase activity, intracellular ROS concentration and mitochondrial membrane potential, of the studied herbal dietary supplements in cells, including A549 human-lung carcinoma cells and rabbit-brain rBCECs cells (a normal cell line to assay the toxic effect on CNS); and (2) to use electron spin resonance oximetry technique to determine the inhibition/induction of lipid peroxidation by the studied herbal dietary supplements in A549 human-lung carcinoma cells and rabbit-brain rBCECs cells.
Use of Electron Spin Resonance Spectroscopy to Characterize the Interactions Between Nanoscale Materials and Model Biological Systems *[Fu]*	***Chemical Reactions:*** (1) To determine if nanomaterials can catalyze Fenton reaction to initiate hydroxyl-radical formation in a nanoparticle-size dependent manner; and (2) to determine if nanomaterials and/or their cations can be reduced by natural-reducing agents, such as ascorbic acid and glutathione, leading to the formation of ROS. ***Microsomal Metabolism Mediated Studies:*** (1) To determine if nanomaterials enhance or inhibit free-radical formation, mediated by microsomal metabolism, in a nanoparticle-size dependent manner; and (2) to determine if nanomaterials and/or their cations can enhance or inhibit microsomal metabolism-mediated lipid peroxidation in a nanoparticle-size dependent manner. ***Cell Culture Studies:*** (1) To determine the toxic effects, including mitochondrial dehydrogenase activity, intracellular ROS concentration, and mitochondrial membrane potential, of nanomaterials of different particle size in cells including A549 human-lung carcinoma cells and rabbit-brain rBCECs cells (a normal cell line to assay the toxic effect on CNS); and (2) To use electron spin resonance oximetry technique to determine the inhibition/induction of lipid peroxidation by nanomaterials of different particle size in A549 human-lung carcinoma cells and rabbit-brain rBCECs cells.
Isolation and Characterization of Fluoroquinolone-Resistant Bacteria from Shrimp *[Nawaz]*	(1) To isolate and identify fluoroquinolone-resistant Gram negative bacteria from shrimp imported from different countries; (2) to perform molecular characterization of fluoroquinolone-resistant determinants; and (3) to perform molecular typing of fluoroquinolone-resistant bacteria.

NCTR/NTP [Project Officer]	Objective and Project Summary
Evaluation of the Applicability of Standard Assays to Genotoxicity of Engineered Nanomaterials *[Chen]*	To assess the activity of four nanoscale materials thought to represent the most common nanomaterials for which human exposure may be expected: nanoscale carbon nanotubes, TiO_2, nanoscale gold, and nanoscale silver in three standard tests required by the FDA (Salmonella Ames test, mouse lymphoma assay, *in vivo* mouse micronucleus assay) and in a new transgenic mutation system (Big Blue® and gpt-delta hybrid transgenic mouse).
Effect of Urinary pH upon the Nephrotoxicity of a Combined Exposure to Melamine and Cyanuric Acid *[Beland]*	To determine the effect of urinary pH upon the renal toxicities elicited by a combined exposure of melamine and cyanuric acid.
FERN Level One Validation Study of a Mobile, Field-Rugged Rapid Detection and Enumeration System for Salmonella in Foods *[Buzatu]*	To conduct a FERN level-one validation for LITMUS Rapid Identification of Bacterial Pathogens (RAPID-B) screening of viable pathogens in food.
Assessment of the Nephrotoxicity of a Seven-Day Combined-Exposure to Melamine and Cyanuric Acid/ Gamboa *[Da Costa]*	To investigate the nephrotoxic effect of a seven-day co-exposure to melamine and cyanuric acid in Fischer 344 rats.
Methylphenidate (Ritalin) Exposure during Pregnancy: Assessment of Neurotoxicity in Rats *[Ferguson]*	To improve the FDA's risk assessment of methylphenidate use during pregnancy as well as provide the animal data needed for more accurate labeling under the proposed guidelines. Overall risk assessment will be improved by the use of the same route of exposure (i.e., oral) as humans, the use of a stress-free delivery method, evaluation of a comprehensive set of behaviors across a wide age-range, the ability to calculate a dose-response, and the documented serum levels of methylphenidate.
Training in Hepatocyte Perfusion and Hepatic-Cell Isolation *[Guo]*	To train member(s) of the Hepatotoxicology Lab in primary liver-cell isolation and culture. The long-term goals will be to obtain signature gene and protein expression patterns of each cell type for comparison to toxin-induced changes. Training must be provided to give confidence in the integrity of liver cells following perfusion, separation, and culture of the liver cells.
Optimization of Oral Dose Administration of Methylphenidate *[Hotchkiss]*	To determine which method for oral dosing of rhesus monkeys will be optimal.
Thermal Stability of Ricin in Fruit Juice *[Tolleson]*	To detect and quantify residual cytotoxic activity present in thermally treated ricin-contaminated fruit juice samples.
Effect of Primary Yogurt Fermentation on the Cytotoxic Activity of the Bioterrorism Agents Ricin and Abrin *[Tolleson]*	To test the applicability of ELISA and cell-based toxicity techniques developed previously to quantify residual ricin and abrin cytotoxic activity when added to yogurt fermentation cultures.
Real-Time PCR Assays for Ricin and Related Potential Bioterrorism Agents in Foods *[Melchior]*	(1) To develop the precise materials and methods needed to perform the proposed assays; (2) to prove that the assays work simply, rapidly, and reliably; and (3) to prove that the assays function as desired in real-world situations, such as with contaminated food stuffs.
Dermal Penetration of Micron- and Nano-scale TiO_2 in Mini Pigs Following Topical Application *[Howard]*	To determine if the nanometer sized TiO_2 penetrate the skin, as determined by analysis of the TiO_2 levels in the skin, lymph nodes, liver, spleen, and kidneys.
Developmental Toxicity of Environmental Contaminants in Folate Deficient Mice - Preliminary Experiment *[Hansen]*	To collect preliminary data for an NIH grant submission that will continue collaboration at Indiana University Medical Center in Indianapolis. The hypothesis is to be examined in the grant is that environmental conditions may cause suboptimal delivery of folic acid to the fetus, which can result in birth defects.

NCTR/NTP [Project Officer]	Objective and Project Summary
Training for Bisphenol A Studies *[Ferguson]*	(1) To develop the appropriate skills and techniques necessary to conduct subsequent studies of developmental treatment with Bisphenol A by training key personnel, including principle investigators, technicians, and animal-care personnel; and (2) to develop techniques, that include complex behavioral assessments and quantitative volumetric analysis of sexually dimorphic brain regions.
Analysis of Blood Pyruvate and Valproic Acid Toxicity in Wistar Han Rats in Response to Dietary Carbohydrate and Calorie Restriction with a High Fat, Moderate, and Low Carbohydrate Diet *[Beger]*	To develop an *in vivo* rat model with lower plasma-pyruvate levels by using dietary carbohydrate restriction. Specific aims are: (1) to determine whether pyruvate blood levels in CR rats fed a HF/LC (high fat/low carbohydrate) diet are decreased by approximately 30% relative to rats fed a balanced diet; (2) to determine whether 45% CR Wistar Han rats can adequately survive on a HF/LC diet for several weeks; and (3) to determine whether CR Wistar Han rats fed a HF/LC diet are more susceptible to valproic acid-induced liver injury than rats fed a balanced healthy diet.
Methods Development for the Evaluation of Estrogen-induced Molecular Changes in Formalin-fixed Parrafin-embedded Rat Prostate *[Delclos]*	To determine the utility of archived formalin-fixed paraffin embedded tissue from past NCTR/NTP studies with estrogenic agents for evaluating gene expression and gene methylation changes that might be biomarkers of adverse effects in prostate and to optimize methods for these analyses.
Interagency Projects (FDA Risk Assessment Issues) *[Chen]*	To track resources expended regarding generic interagency projects involving FDA risk assessment issues.
Modification and Application of Quantitative Risk Assessment Techniques to FDA-regulated Products *[Chen]*	To track resources expended regarding generic interagency projects involving FDA risk assessment issues.
Application of Biometrical Procedures for NTP Projects *[Chen]*	In response to requests from NCTR scientists, modify and/or apply statistical techniques to the design, conduct, analysis, and interpretation of NTP studies to identify and assess the cancer and noncancer risks of potentially toxic substances.
Pathology Training and Methods Development *[Witt]*	To train new employees for necropsy, histopathology, and orbital bleeding techniques.
Counter-Terrorism Planning and Support *[Slikker]*	To develop means of collecting time and resources spent on counter-terrorism planning and support efforts.
Development and Maintenance of Double Transgenic Mutation Target Mouse Colonies: X-G (PhiX174 and gpt-delta in C57Bl/6) and XGHA (Double Transgenic Mutation Target, Hairless Albino in C57Bl/6) *[Manjanatha]*	To maintain a breeding colony of transgenic mice for the purpose of testing this mouse as a new *in vivo* model for genotoxicity testing. The breeding colony will provide homozygous mice to breed with CH3 mice in order to produce C57H3F1, which is the standard NTP mouse. These F1 will be used in future protocols to test compounds other than ENU, which was tested under protocol E06977.01. This project is requested to maintain the colony from which future protocols will conduct the cross-breeding.
Human Studies of Isoflavone Safety and Efficacy *[Doerge]*	For bioanalytical analysis of soy isoflavones (and metabolites) in support of clinical trials at the University of Miami and Wayne State University.
General NCTR Support for the Center for Phototoxicology *[Howard]*	To provide support for the Center for Phototoxicology resources expended with NCTR funding.

NCTR/NTP [Project Officer]	Objective and Project Summary
General Support for Center for Functional Genomics *[Fuscoe]*	The Center for Functional Genomics is a centralized facility to handle all aspects of microarray printing and processing. Its objectives are: (1) to provide NCTR investigators with access to high quality microarray technology for the investigation of biological mechanisms of action underlying the toxicity of products regulated by the FDA, and related fundamental and applied research; (2) to create a validated toxicogenomics database that will be a resource for the scientific and regulatory community; (3) to be a focal point and scientific resource for issues in toxicogenomics; and and (4) to utilize advances in genomics to address issues critical to the FDA mission. The Center for Functional Genomics will provide continual development of new and better approaches to microarray technologies including larger gene collections, custom microarrays, validated gene expression databases, experimental design, and tools for handling and analyzing microarray data.
General Support for Center for Toxicoinformatics *[Tong]*	Provide toxicoinformatics support for the center-wide research.
General Support for Center of Hepatotoxicology *[Guo]*	Provide hepatotoxicology support for the center-wide research.
Mass Spectrometry and Proteomics Collaborations *[Yu]*	Provide mass spectroscopy and proteomics support for the center-wide research.
Maintenance, Calibration and Repair for Mass Spectrometry and Proteomics *[Yu]*	Provide NCTR proteomic support.
Genetic Toxicology Evaluations in Support of FDA Centers for Evaluating Substances for their Genotoxic Potential *[Moore]*	To provide direct research to FDA Centers.
Biostatistical Modeling for Food Protection Plan *[Chen]*	Build a team to enhance modeling capability for relative risk ranking.
NCTR/Arkansas Regional Laboratory-Office of Regulatory Affairs Nanotechnology Core Facility – FDA SUPPORT *[Howard]*	To support the needs of NCTR to characterize nanoscale materials used in toxicology tests, to detect these materials in biological samples, and to support the needs of Arkansas Regional Laboratory-Office of Regulatory Affairs to detect and characterize nanoscale materials in FDA regulated products.

NIEHS/NTP

NIEHS/NTP

Photo courtesy of Steve McCaw

Realignment

The NTP, within the NIEHS Division of Intramural Research, underwent a realignment of the program on October 28, 2007. The goal of these changes was to give a clearer identity to the activities, staff, and resources associated with the NTP and to provide greater transparency to the NTP budget, physical location, capabilities and mission. The realignment provided a scaffold to meet the goals described in the NTP Roadmap and to allow a continuation of the traditional testing and assessment activities under the purview of the NTP. John Bucher, Ph.D. is NTP Associate Director and remains as operational manager of NTP activities. Mary Wolfe, Ph.D. was appointed the Deputy Program Director for Policy and Nigel Walker, Ph.D. was appointed Deputy Program Director for Science. NTP's position within the NIEHS organizational structure may be found at *http://www.niehs.nih.gov/about/orgstructure/orgchart.cfm*. This reorganization was specific for NTP at NIEHS and did not affect NIOSH and NCTR NTP staff and activities. Tables 5 and 6 describe the offices or centers and the five branches created under the realignment.

Communication and Public Outreach

Maintaining open communications and ensuring dialogue with federal and state agencies, industry, nongovernment groups, academia, and the public are goals of the NTP. NTP advisory groups (see page 6) provide regular scientific and public peer review and input. NTP conferences and workshops remain a priority and are designed to bring researchers, regulators, policy makers, and the public together to examine issues and achieve consensus on future directions in toxicology and risk assessment.

Distribution of NTP study results, program plans, initiatives, announcements, press advisories, and publications is accomplished in a variety of ways to communicate as much as possible with the public.

Table 5: The NTP Program Office at NIEHS is comprised of five offices or centers		
Office/Center	**Director**	**Function**
Office of Nomination and Selection	Scott Masten, Ph.D.	Solicits the nomination of studies that permit the testing of hypotheses to enhance the predictive ability of future NTP studies, address mechanisms of toxicity, or fill significant gaps in the knowledge of the toxicity of chemicals or classes of chemicals.
Report on Carcinogens	C.W. Jameson, Ph.D. (ret'd February 2008)/ Ruth Lunn, D.Phil.	Prepares the congressionally mandated RoC, which identifies substances, mixtures of chemicals, or exposures that cause or might cause cancer and to which a significant number of persons in the United States are exposed.
NTP Interagency Center for the Evaluation of Alternative Toxicological Methods	RADM William Stokes, D.V.M.	Evaluates alternative toxicological methods, promoting their validation and regulatory acceptance with the goal of refining, reducing, and/or replacing animal use; provides technical, scientific, and administrative support for the ICCVAM.
Center for the Evaluation of Risks to Human Reproduction	Michael Shelby, Ph.D.	Provides scientifically based, uniform assessments of the potential for adverse effects on reproduction and development caused by agents to which humans may be exposed.
Office of Liaison, Policy and Review	Mary Wolfe, Ph.D.	Provides oversight and management of activities related to scientific review, science policy, and communication; activities include managing and overseeing the NTP's external advisory groups, compiling information and coordinating responses to outside inquiries, serving as liaison to bring interested parties together to exchange information through workshops and other events, preparing and disseminating information about the NTP and its activities, and representing the NTP through exhibits at national and international events.

Information is routinely distributed to interested parties through Federal Register announcements and on the NTP website (*http://ntp.niehs.nih.gov*). The website offers access to information about the program that details and highlights ongoing and future initiatives, announcements, NTP centers, NTP publications, and study data. The public can subscribe to the NTP ListServ on the website to receive news and updates. There are currently over 4000 subscribers to the ListServ. The NTP publishes a quarterly newsletter, the *NTP Update*, which can be downloaded from the NTP website. NTP actively participates in the annual Society of Toxiology meeting. At the 2008 meeting in Seattle, WA, NTP staff participated in one platform session, one roundtable, three workshops, three symposia, and 20 posters. Ten NTP staff participated as experts in the "Meet the Experts" session at the meeting.

The NIEHS/NTP Central Data Management (CDM) Office oversees distribution (upon request) of specific, chemical study information, and printed NTP documents – the NTP study status reports, final and draft copies of NTP Technical Report Series, and background documents for substances nominated to the NTP. During FY 2008, CDM handled over 200 requests for technical reports and other NTP publications. On-line, searchable access is available for the Report on Carcinogens (*http://ehponline.org*) and the NTP Technical, Toxicity, and Genetically Modified Models Series Report Series (*http://ntp.niehs.nih.gov* or *http://ehp.niehs.nih.gov/ntp/docs/ntp.html*).

Table 6: Five branches within the NTP were created under the realignment		
Branch	**Chief**	**Function**
Biomolecular Screening Branch	Raymond Tice, Ph.D.	Develops high- and medium-throughput screening activities; identifies and evaluates *in vitro* and cell based high-throughput assays as tools useful for screening and prioritizing chemicals for toxicity testing; carries out NTP automated screening of *Caenorhabditis elegans*.
Cellular and Molecular Pathology Branch	Robert Sills, D.V.M., Ph.D.	Provides support for NTP pathology and program archives and for pathology investigations by intramural NIEHS researchers.
Host Susceptibility Branch	John (Jef) French, Ph.D. (Acting)	Plans, conducts, and analyzes assessments of chemical toxicity in multiple murine strains; fosters collaborations among the NTP and intramural and extramural investigators; and fosters public-private partnerships to examine the genetic basis of response to environmental exposures and the clinical manifestations of resulting disease states.
Program Operations Branch	Cynthia Smith, Ph.D. (Acting)	Oversees activities that support NTP research and testing including chemistry activities, studies related to absorption, distribution, metabolism, and excretion, and quality assurance, maintenance and development of data capture and retrieval systems, the central data repository, and the NTP website.
Toxicology Branch	Paul Foster, Ph.D. (Acting)	Designs and oversees NTP toxicology studies integrating the findings with toxicokinetics and toxicogenomics.

The NTP is interested in and welcomes stakeholder input into its programs and priorities. Nominations, inquiries, and comments from the public and other interested parties are encouraged at any time. The NTP Office of Liaison, Policy and Review at the NIEHS under the direction of Dr. Mary S. Wolfe serves as the focal point for receiving input to the program and for overseeing the distribution of information about programs, workshops, initiatives, etc.

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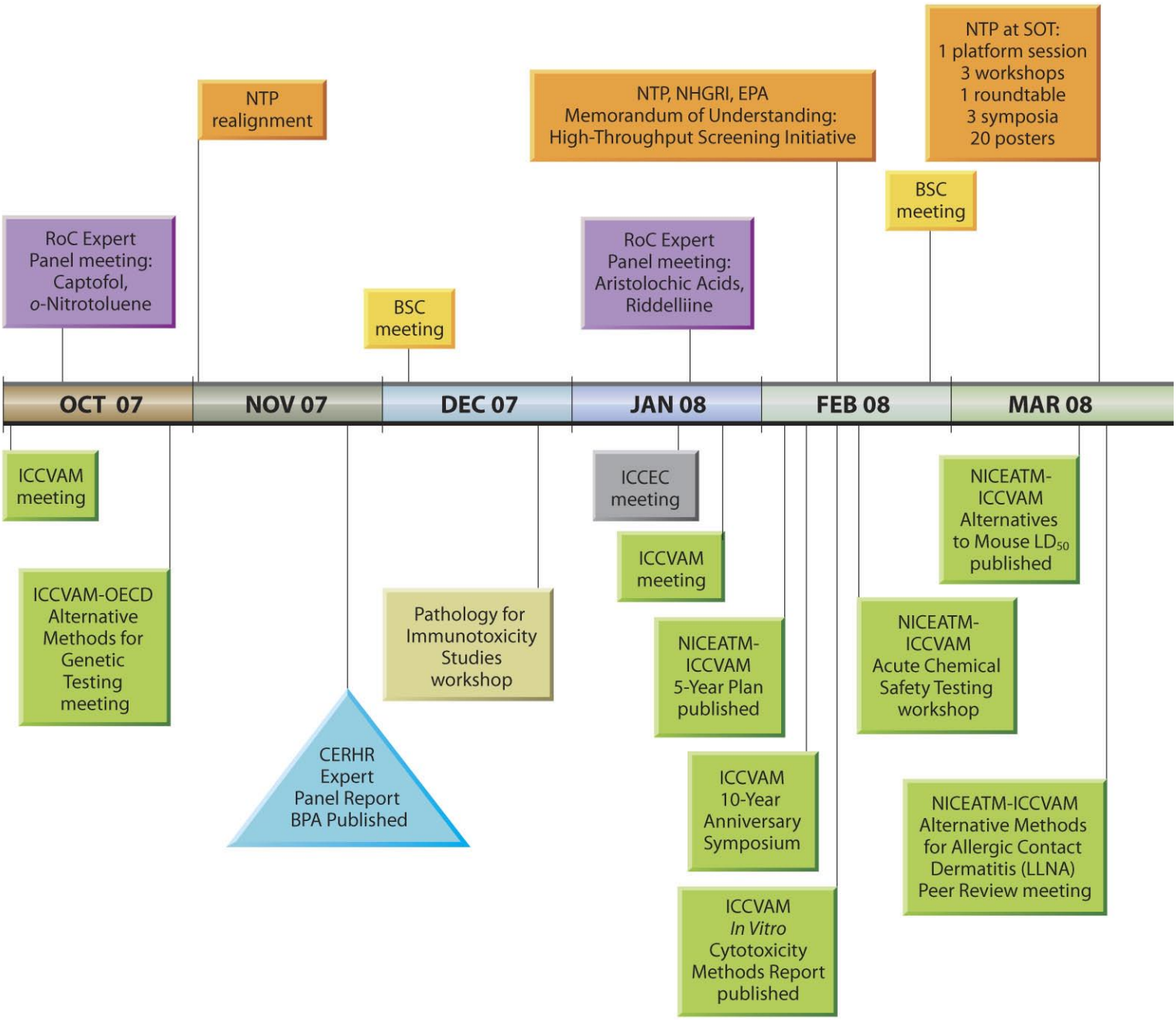
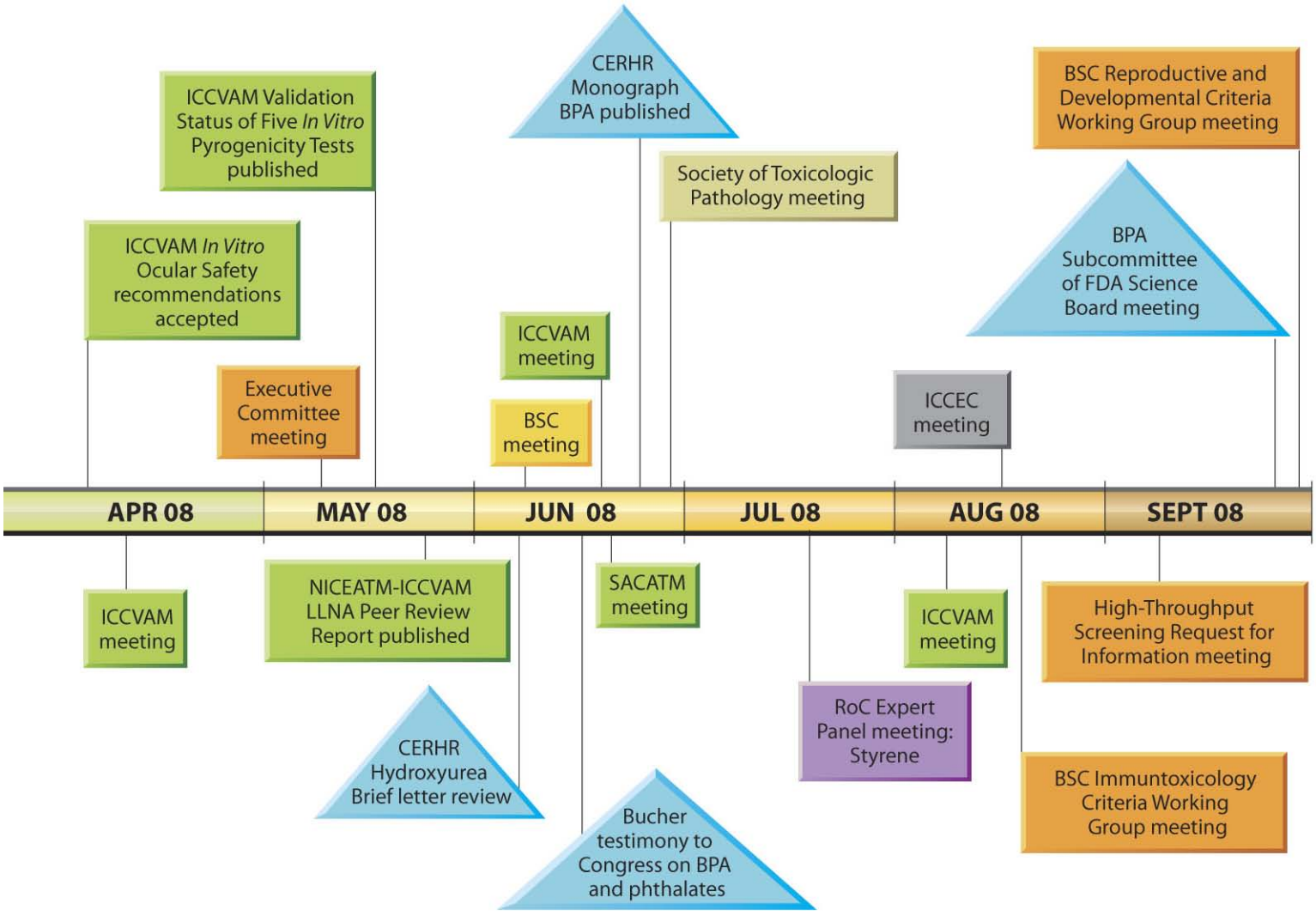
FY 2008 Highlights





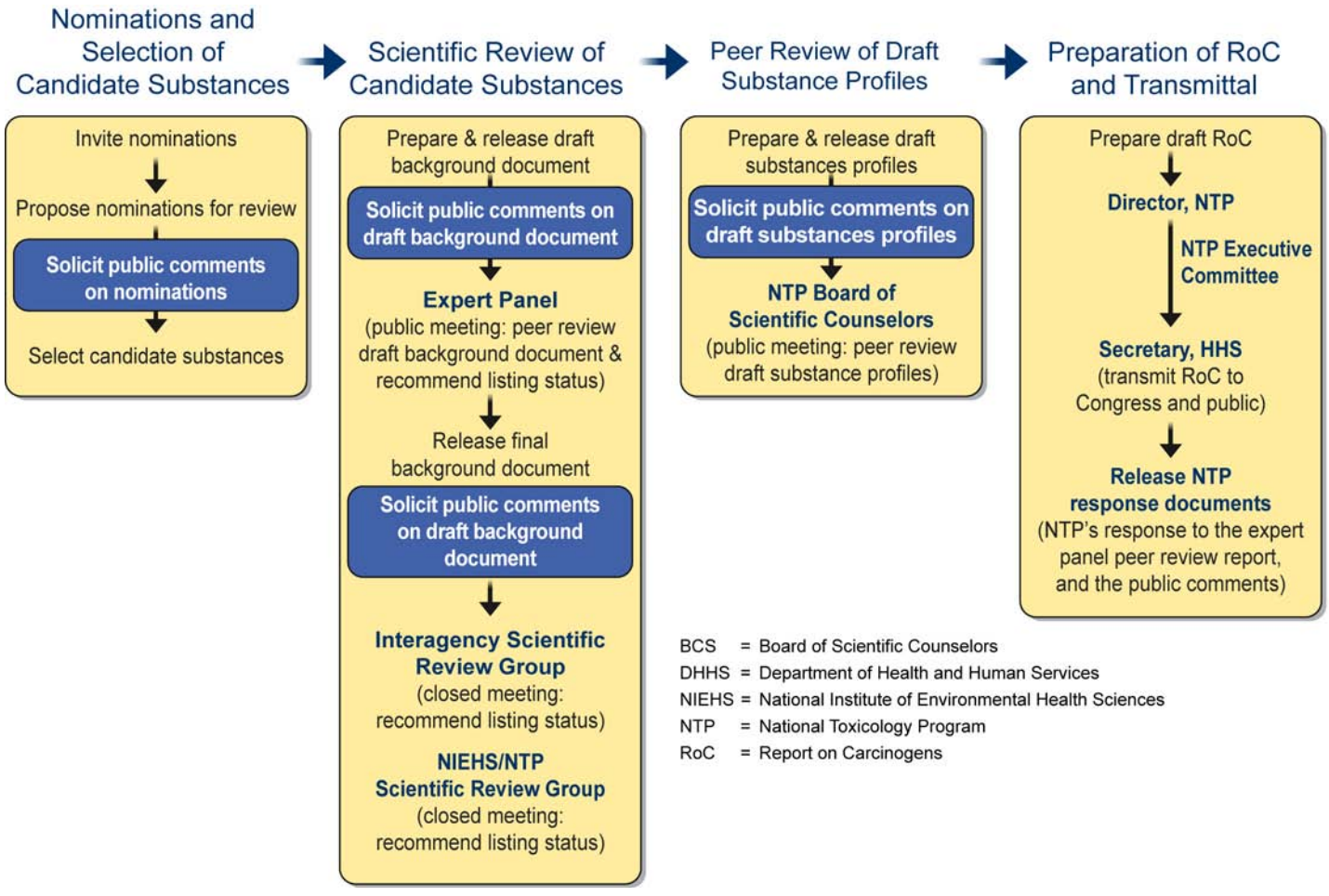
BPA	bisphenol A
BSC	NTP Board of Scientific Counselors
CERHR	Center for the Evaluation of Risks to Human Reproduction
ICCEC	Interagency Committee for Chemical Evaluation and Coordination
ICCVAM	Interagency Coordinating Committee for the Validation of Alternative Methods
LLNA	Local Lymph Node Assay
NHGRI	National Human Genome Research Institute
NICEATM	NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
OECD	Organisation for Economic Cooperation and Development
RoC	Report on Carcinogens
SACATM	Scientific Advisory Committee on Alternative Toxicological Methods
SOT	Society of Toxicology

Report on Carcinogens

The Report on Carcinogens (RoC) is a congressionally mandated listing [Section 301(b)(4) of the Public Health Services Act, 42 U.S.C. 241(b)(4)] of substances (1) that either are known to be human carcinogens or may reasonably be anticipated to be human carcinogens; and (2) to which a significant number of persons residing in the United States are exposed. The Secretary of Health and Human Services has delegated preparation of the RoC to the NTP, with assistance from other federal health and regulatory agencies.

The RoC is an informational, scientific, and public health document that identifies and discusses agents, substances, mixtures, or exposure circumstances that may pose a carcinogenic hazard to human health. It serves as a meaningful and useful compilation of data for listed compounds on (1) the carcinogenicity, genotoxicity, and biological mechanisms in humans and/or animals, (2) the potential for exposure, and (3) any relevant regulations promulgated by federal agencies. Dr. C. W. Jameson directed preparation of the RoC until his retirement in February, 2008. Dr. Ruth Lunn, NIEHS/NIH, now oversees preparation of the RoC. The Constella Group is contracted to provide support for preparation of the RoC.

Figure 3: NTP Report on Carcinogens Review Process



A new process (Figure 3) for preparation of the RoC was initiated on April 16, 2007, to enhance the scientific development of the RoC and address guidance from the Office of Management and Budget Information Quality Bulletin for Peer Review. Information about this process can be found at *http://ntp.niehs.nih.gov/go/15208*. The two important new elements in the 12th RoC review process are (1) the public peer review of draft background documents by *ad hoc* scientific expert panels and (2) the public peer review of draft substance profiles by the NTP BSC.

This process for review of nominations to the report is a multi-step, formal, and open process as shown in the diagram above. The nomination of substances for listing in or removal from the RoC is open to all interested individuals and groups. For each substance under review, the NTP convenes an expert panel, selected from recognized experts in relevant scientific disciplines, to peer review the draft background document and make a recommendation for listing status in the RoC at a public meeting. Following the meeting, the expert panel's recommendation and scientific justification for the recommendation are released for public comment, and the draft background document is finalized based on NTP's review of the peer-review comments and public comments. The Interagency Scientific Review Group and the NIEHS/NTP Scientific Review Group each convene a closed meeting to provide an independent recommendation for listing status. Taking into account the recommendations from the three review groups, and the public comments, the NTP drafts a substance profile, which contains its preliminary listing status recommendation, the science that supports the recommendation, and information on use, production, exposure and current regulations. The NTP BSC then meets publicly to review the draft substance profile. Public comments are solicited multiple times during the process and provided to each review group as available. The NTP then prepares the draft RoC (which contains substance profiles for newly (proposed) listed substances and substances listed in previous editions of the RoC) for review and comment by the NTP Executive Committee. The NTP Director receives the input from all reviews plus the public comments and submits the final draft RoC to the Secretary, DHHS, for review and approval.

Scientific review of nominations to the 12th edition began in FY 2007. The RoC Center convened three expert panels to review draft background documents for five chemicals, make a recommendation regarding the listing of those chemicals in 12th RoC, and provide a scientific justification for those recommendations. The expert panels recommended listing styrene, captofol, *ortho*-nitrotoluene, and riddelliine each as *reasonably anticipated to be a human carcinogen*. The expert panel recommended listing aristolochic acids as *known to be human carcinogens*.

Table 7: Candidate Substances for the 12th Report on Carcinogens (as of December 2008)

Candidate Substance [CASRN] Nominator	Primary Uses/Exposures	Basis of Nomination
Aristolochic acids [313-6 7-7] NIEHS	The principle extract from Aristolochia; a mixture of nitrophenanthrene carboxylic acids; used in traditional Chinese medicine as anti-rheumatics, as diuretics, in the treatment of edema and for other conditions such as hemorrhoids, coughs and asthma.	IARC finding of sufficient evidence of carcinogenicity in animals and limited evidence in humans. (IARC Monograph Vol. 82, 2002).
Captafol [2425-06-01] NIEHS	A fungicide that has been widely used since 1961 for the control of fungal diseases in fruits, vegetables and some other plants. Use of captafol in the United States was banned in 1999.	IARC finding of sufficient evidence of carcinogenicity in animals (IARC Monograph Vol. 53, 1991). IARC also noted that captafol is positive in many genetic assays, including the *in vivo* assay for dominant lethal mutation.

Candidate Substance [CASRN] Nominator	Primary Uses/Exposures	Basis of Nomination
Cobalt–tungsten carbide powders and hard metals NIEHS	Are manufactured by a process of powder metallurgy from tungsten and carbon (tungsten carbide), and small amounts of other metallic compounds using cobalt as a binder. They are used to make cutting and grinding tools, dies, and wear products for a broad spectrum of industries including oil and gas drilling, and mining.	Recent human cancer studies on the hard metal manufacturing industry showing an association between exposure to hard metals (cobalt tungsten-carbide) and lung cancer.
Di-(2-ethylhexyl) Phthalate (DEHP) [117-81-7] Aekyung Petrochemical Co., LTD of Seoul, Korea	Used as a plasticizer in polyvinyl chloride (PVC) resins for fabricating flexible vinyl products. PVC resins have been used to manufacture toys, dolls, vinyl upholstery, tablecloths and many other products. Currently listed in the RoC as reasonably anticipated to be a human carcinogen.	IARC reclassified as not classifiable as to its carcinogenicity to humans (Group 3) (IARC Monograph Vol.77, 2000), stating that there was sufficient evidence for the carcinogenicity in experimental animals; however, the mechanism for liver tumor involves peroxisome proliferation that is not relevant to humans. Nominated for delisting.
Formaldehyde [50-00-0] NEIHS – for reclassification	Primarily used in the production of resins that are used in the production of many different products, including plastics, adhesives and binders for wood products, pulp and paper, synthetic fibers, and in textile finishing. It is also used as a disinfectant and preservative and as an intermediate for many industrial chemicals.	Nominated for reconsideration based on the 2004 IARC2 review, which concluded that there was sufficient evidence for the carcinogenicity of formaldehyde in humans (IARC Monograph Vol. 88, 2004).
Certain glass wool fibers North American Insulation Manufacturers Association nominated glass wool (respirable size) for removal from RoC	Glass wool fibers, which are a type of synthetic vitreous fibers, are an inorganic fibrous material manufactured primarily rom glass and processed finorganic oxides. The composition of these fibers may vary substantially because of differences in end-use, manufacturing requirements and biopersistence considerations. The major uses of glass wool are in thermal, electrical, and acoustical insulation, weatherproofing, and filtration media. Some glass wool fibers (special purpose fibers) are used for high-efficiency air filtration media, and acid battery separators.	Insulation glass wool: IARC finding of limited evidence of carcinogenicity in animals and evaluation as not classifiable as to its carcinogenicity to humans (Group 3) (IARC Monograph Vol. 81, 2002). Special-purpose glass IARC finding of sufficient evidence of carcinogenicity in animals. (IARC Monograph Vol. 81, 2002).
Etopside [33219-42-9]	A DNA topoisomerase II inhibitor used in chemotherapy for non-Hodgkin's lymphoma, small-cell lung cancer, testicular cancer, lymphomas, and a variety of childhood malignancies.	IARC finding of limited evidence of carcinogenicity humans. (IARC Monograph Vol. 76, 2000).
Etopside in combination with cisplatin and bleomycin	Etoposide in combination with cisplatin and bleomycin is used to treat testicular germ cell cancers.	IARC finding of sufficient evidence of carcinogenicity in humans (IARC Monograph Vol. 76, 2000).

Candidate Substance [CASRN] Nominator	Primary Uses/Exposures	Basis of Nomination
Metal working fluids NIEHS	Complex mixtures that may contain mixtures of oil, emulsifiers, anti-weld agents, corrosion inhibitors, extreme pressure additives, buffers biocides and other additives. They are used to cool and lubricate tools and working surfaces in a variety of industrial machining and grinding operations.	Recent human cancer studies of metal working fluids that show an association between exposure to these materials and cancer at several tissue sites.
ortho-Nitrotoluene [88-72-2] NIEHS	Used to synthesize agricultural and rubber chemicals, azo and sulfur dyes, and dyes for cotton, wool, silk, leather, and paper.	Results of a NTP bioassay (NTP Technical Report 504, 2003), which reported *clear evidence of carcinogenic activity* in male and female rats and mice.
Riddelliine [88-72-2] NIEHS	Found in a class of plants growing in western United States. Cattle, horses and sheep ingest these toxic plants. Residues have been found and in, milk, and honey.	Results of a NTP bioassay (NTP Technical Report 508, 2003), which reported *clear evidence of carcinogenic activity* in male and female rats and mice.
Styrene [100-42-5] Private Individual	Used in the production of polystyrene, acrylonitrile-butadiene-styrene resins, styrene-butadiene rubbers and latexes, and unsaturated polystyrene resins.	IARC finding of limited evidence of carcinogenicity in animals and limited evidence of carcinogenicity in humans (IARC Monograph Vol. 82, 2002).
Teniposide [29767-20-2] NIEHS	Teniposide is a DNA topoisomerase II inhibitors used mainly in the treatment of adult and childhood leukemia.	IARC finding of limited evidence of carcinogenicity in humans (IARC Monograph Vol. 76, 2000).

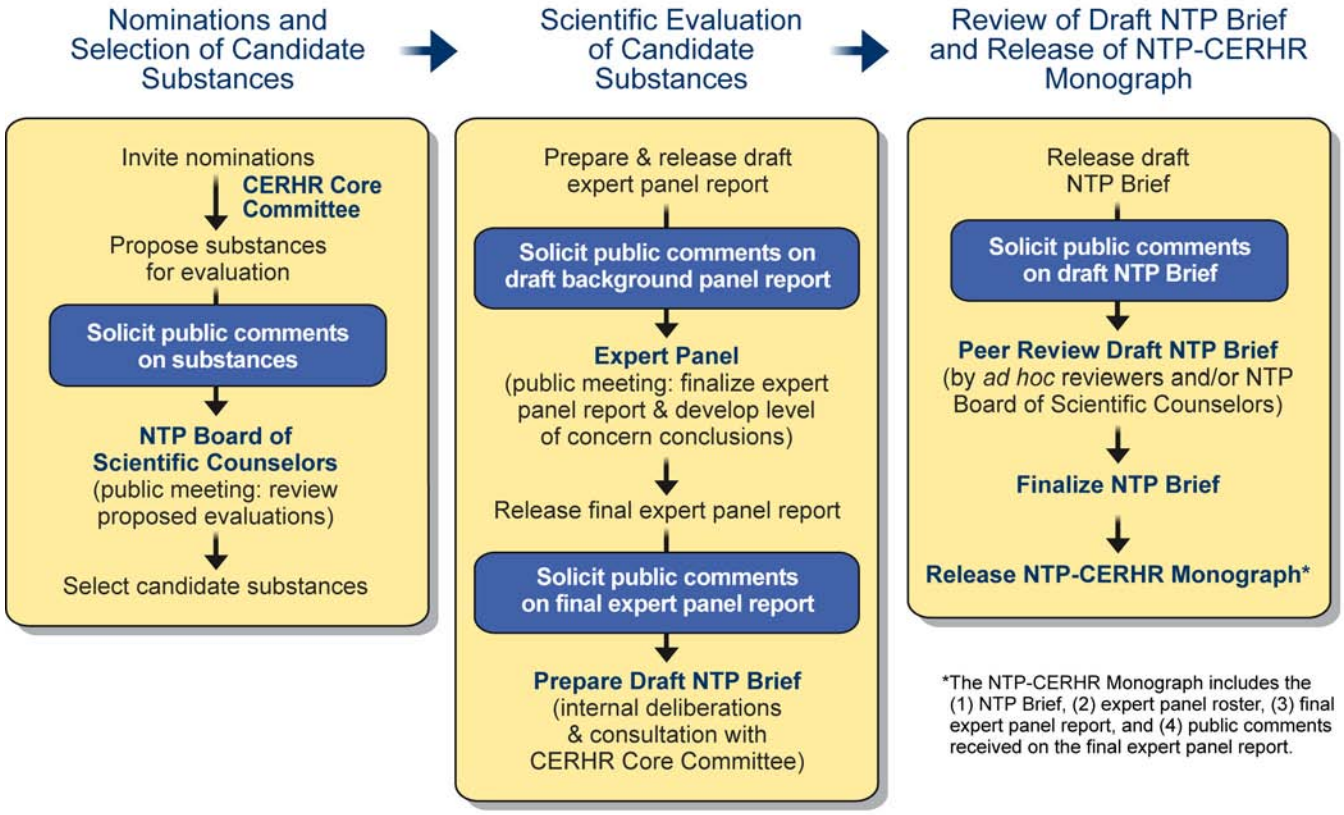
International Agency for Research on Cancer (IARC). IARC Monographs are available from http://monographs.iarc.fr/. NTP Technical Reports are available at http://ntp.niehs.nih.gov/ see "NTP Study Reports."

Contact Information: Report on Carcinogen Center, Dr. Ruth Lunn, *lunn@niehs.nih.gov.*
RoC website: *http://ntp.niehs.nih.gov* select "Report on Carcinogens."

Center For the Evaluation of Risks to Human Reproduction

The Center for the Evaluation of Risks to Human Reproduction (CERHR) was established in 1998 to serve as an environmental health resource to the public and regulatory and health agencies. CERHR is located at the NIEHS and Dr. Michael Shelby served as director in FY 2008. CERHR publishes monographs that assess the potential for substances to cause adverse effects on reproduction and development in humans. The BSC (see page 6) advises CERHR on its processes, priorities, and direction.

Figure 4. Center for the Evaluation of Risks to Human Reproduction (CERHR) Evaluation Process



CERHR follows a formal process (Figure 4) for nomination, selection, and evaluation of substances that includes evaluation by an *ad hoc* panel of scientists with topic-specific expertise and three formal solicitations of public comment. CERHR selects substances for evaluation based on several factors including production volume, extent of human exposures, public concern about the chemical hazard, and the extent of published data from reproductive or developmental toxicity studies. The NTP Board of Scientific Counselors provides oversight for CERHR and offers advice on priorities, directions, and the adequacy of the Center's process. The Core Committee is an advisory body consisting of scientists who represent government agencies that participate on the NTP Executive Committee.

CERHR convenes an expert panel whose meetings are open to the public. Following completion of an expert panel report and receipt of public comments on the report, CERHR prepares a draft NTP Brief, in which the NTP considers all public comments and any additional scientific information available following completion of the expert panel's deliberations and report. The NTP distributes the draft NTP Brief to the CERHR Core Committee for review and comment. The CERHR posts the draft NTP Brief on its website, announces its availability, and requests public comments on the document in a Federal Register notice. The draft NTP Brief then undergoes peer-review. The NTP Brief provides in plain language:

- background information on the chemical
- the findings of the expert panel report
- discussion of any relevant data received after the expert panel meeting
- the NTP's conclusions on the potential for the chemical to cause adverse reproductive and/or developmental effects in exposed humans

Once the NTP Brief is final, CERHR prepares a monograph that is transmitted to federal and state agencies, interested parties, the public, and is published in MEDLINE. Each NTP-CERHR monograph includes the expert panel's report, the NTP Brief, and any public comments received on the expert panel report.

Additional details about the CERHR process, CERHR expert panel evaluations, and monographs are available at the CERHR website (*http://cerhr.niehs.nih.gov*). The CERHR website also contains information covering common questions and concerns regarding a healthy pregnancy and the potential of various exposures to adversely affect fertility or the development of children. CERHR focused on two chemicals in FY 2008, bisphenol A (BPA) and hydroxyurea. The timelines for those evaluations are shown in Tables 8 and 9.

Bisphenol A (CASRN 80-5-07) BPA is a high production volume chemical used primarily in the production of polycarbonate plastics and epoxy resins. Exposure to the general population can occur through direct contact with BPA or by exposure to food or drink that has been in contact with a material containing bisphenol A. CERHR selected this chemical for evaluation because of (1) high production volume, (2) widespread human exposure, (3) evidence of reproductive toxicity in laboratory animal studies, and (4) public concern.

The NTP BPA evaluation received considerable public and media attention with over 2000 articles published and NTP staff conducted approximately 100 media interviews. NTP was involved in two national activities regarding BPA in FY 2008. On June 10, 2008, Dr. John Bucher presented NIEHS Testimony to the Subcommittee on Commerce, Trade & Consumer Protection, U.S. House of Representatives Committee on Energy & Commerce on BPA and phthalates.

NTP also participated in the BPA Subcommittee of the Science Board to the Food and Drug Administration on September 18, 2008, in Washington, DC. The subcommittee discussed the FDA's draft assessment

of BPA for use in food contact applications. Dr. Bucher presented the weight of evidence from the NTP evaluation that BPA causes adverse developmental or reproductive effects in humans and in laboratory animals. Specific discussion points presented were: (1) human exposure assessment, (2) mechanistic assumptions, (3) metabolism and route of exposure considerations, (4) developmental effects on brain/behavior, prostate, and mammary gland, and (5) effects on puberty and sexual maturation. In summary, low dose BPA studies done in laboratory animals provide limited evidence for adverse effects. These effects occur at BPA exposure levels similar to those experienced by humans; therefore, the possibility that BPA may alter human development cannot be dismissed. More research is needed to better understand their implications for human health.

Hydroxyurea (CASRN 127-07-1) Hydroxyurea is used in the treatment of cancer, sickle cell disease, and thalassemia. It is the only treatment for sickle cell disease used in children aside from blood transfusion. Hydroxyurea may be used in the treatment of children and adults with sickle cell disease for an extended period of time or for repeated cycles of therapy. CERHR selected hydroxyurea for expert panel evaluation because of (1) increasing use in the treatment of sickle cell disease in children and adults, (2) knowledge that it inhibits DNA synthesis and is cytotoxic, and (3) published evidence of reproductive and developmental toxicity in rodents.

Table 8: Timeline for the BPA Evaluation

Date and/or Location	Steps in Process for Evaluation of BPA
December 2005	Announcement of intention to conduct an evaluation of the potential for BPA to cause adverse effects on reproduction and development in humans
December 12, 2006	Announcement of availability of Draft Expert Panel Report on BPA, request for public comment on report, and public meeting to review draft
March 5-7, 2007/ Alexandria, VA	Expert Panel Meeting – 14 experts met and were unable to complete the review and assessment of over 500 studies
April 2007	Interim draft report published
August 6-8, 2007/ Alexandria, VA	Second Expert Panel Meeting – 12 experts met and drew conclusions on effects in pregnant women and fetuses, infants and children, and adults
November 26, 2007	CERHR Expert Panel Report on Reproductive and Developmental Toxicity of Bisphenol A published
April 15, 2008	Release of draft NTP Brief on BPA
June 11, 2008/ Research Triangle Park, NC	Peer review of draft NTP Brief on BPA at BSC meeting
September 3, 2008	NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of BPA published. The NTP expressed: • *some concern for effects* on the brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures to BPA • *minimal concern for effects* on the mammary gland and an earlier age for puberty for females in fetuses, infants, and children at current human exposures to BPA • *negligible concern that exposure* of pregnant women to BPA will result in fetal or neonatal mortality, birth defects, or reduced birth weight and growth in their offspring • *negligible concern that exposure* to BPA will cause reproductive effects in non-occupationally exposed adults and minimal concern for workers exposed to higher levels in occupational settings

For FY 2009 CERHR has plans to update evaluations of the scientific evidence regarding the potential reproductive and/or developmental toxicity associated with exposure to genistein and soy formula. CERHR convened an expert panel in 2006 to conduct evaluations of the potential toxicities of these substances. The expert panel reports were published in 2006, but CERHR did not complete the briefs or issue NTP-CERHR monographs. Since 2006, a substantial number of new publications related to the health effects of genistein and soy formula have been published. Because of the substantial new literature on these substances, CERHR plans an updated expert panel evaluation of these substances. A recent Federal Register notice published October 8, 2008, announced this plan and requested submissions of information about ongoing studies or upcoming publications on these substances and for nominations of scientists to serve on an expert panel.

Contact Information: Center for the Evaluation of Risks to Human Reproduction, Dr. Michael Shelby, Director, *shelby@niehs.nih.gov.* CERHR website: *http://cerhr.niehs.nih.gov*

Table 9: Timeline for the Hydroxyurea Evaluation

Date and/or Location	Steps in Process for Evaluation of Hydroxyurea
November 2006	Draft NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Hydroxyrurea published
January 24-26, 2007/ Alexandria, VA	Expert panel evaluation by 13 independent scientists producing the NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Hydroxyurea
March 17, 2008	Draft NTP Brief on Hydroxyurea published, concluding that NTP: • expresses *serious concern* that exposure of men to therapeutic doses may adversely affect sperm production • concurs with the Expert Panel that there is *concern* that exposure of pregnant women to hydroxyurea may result in birth defects or abnormalities of fetal growth and postnatal development in their offspring • concurs with the Expert Panel that there is *minimal concern* that exposure of children to therapeutic doses of hydroxyurea at 5-15 years of age will adversely affect growth
June 2008	External letter peer-review of draft NTP Brief on Hydroxyurea by four experts (publication of brief due in October 2008)

NTP Interagency Center For The Evaluation of Alternative Toxicological Methods

The development, validation, acceptance, and harmonization of new, revised, and alternative toxicological test methods are coordinated in the Federal government through ICCVAM). NIEHS established ICCVAM in 1997 to implement a directive in the 1993 NIH Revitalization Act to develop a process to achieve the regulatory acceptance of scientifically valid alternative testing methods. Alternative methods are those methods that reduce, refine, or replace the use of animals. NICEATM was established in 1998 to administer ICCVAM and provide scientific support for ICCVAM activities. The ICCVAM Authorization Act of 2000 (42 U.S.C. 285*l*-3) established ICCVAM as a permanent interagency committee under NICEATM, and specified the purposes and duties of the committee. Dr. William Stokes (RADM, USPHS) is the NICEATM Director and Executive Director of the ICCVAM. The Integrated Laboratory Systems, Inc., is the contractor that provides support for NICEATM.

ICCVAM and NICEATM work to promote the validation and regulatory acceptance of new, revised, and alternative toxicological test methods that are more predictive of human and ecological effects than those currently available and that refine, reduce, and replace animal use whenever possible. The desired outcomes from these new methods are to improve agencies' abilities to assess risk and make regulatory decisions, promote more humane animal use, and reduce replace animal usage. NICEATM in conjunction with ICCVAM, convenes scientific peer review panels to evaluate the validation status of proposed alternative testing methods for which there is evidence of scientific validity. ICCVAM then develops formal test method recommendations for consideration of acceptance by agencies. NICEATM and ICCVAM also convene workshops and expert panels to evaluate the adequacy of existing methods, identify promising test methods for further development and validation, evaluate the interim validation status of methods, and evaluate proposed validation studies.

NICEATM receives test method nominations or submissions intended for ICCVAM consideration and review (see *http://iccvam.niehs.nih.gov/*). Test methods can be nominated for validation studies or technical reviews. The ICCVAM evaluation process involves an initial assessment by NICEATM of the adequacy and completeness of the test method nomination or submission, and a determination by ICCVAM of the priority of the proposed method for technical evaluation or validation studies. Once a proposed test method is accepted for evaluation or validation, ICCVAM assembles an interagency working group of scientists with appropriate scientific and regulatory expertise to collaborate with NICEATM on the evaluation process. Depending on the validation status of the proposed test method, ICCVAM, in conjunction with NICEATM, develops recommendations and priorities for appropriate evaluation activities. Such efforts might include an expert workshop, an expert panel meeting, a peer review meeting, an expedited peer review process, or a validation study. Information and status for the following NICEATM activities, including meeting reports, and background documents, are available on the NICEATM-ICCVAM website. Recent NICEATM publications, meetings, and test methods currently under review, and recommendations are presented in Tables 10, 11, 12, and 13 respectively.

The NICEATM-ICCVAM Ten-Year Anniversary Symposium, with over 100 attendees, was held on February 5, 2008, at the CPSC headquarters in Bethesda. A panel discussion "Test Method Research, Development, Translation and Validation: The Way Forward for ICCVAM and its Stakeholders," included members from government, industry, academe, animal protection, SACATM, ECVAM, JaCVAM, and the NTP Executive Committee. ICCVAM's accomplishments were highlighted at the symposium, including the 17 alternative methods accepted or endorsed by regulatory agencies since 1999. Other accomplishments included developing recommendations for research, development, translation, and validation activities

for various alternative test methods; developing international guidance on test method validation and acceptance criteria and processes; defining and establishing a process for development of performance standards; and establishing and strengthening international partnerships with European Centre for the Validation of Alternative Methods (ECVAM) and Japanese Center for the Validation of Alternative Methods (JaCVAM).

The NICEATM-ICCVAM Five-Year Plan, a blueprint for advancing alternative methods that will reduce, refine (less pain and distress), and replace the use of animals in testing (the 3Rs), was unveiled at the symposium. Prepared in response to a request from Congress, the plan identifies priority areas for research, development, translation, and validation activities needed to support the regulatory acceptance of alternative test methods. The four areas of highest priority are safety tests for ocular (eye) injuries, dermal (skin) damage, and acute poisoning and tests for biologics such as vaccines. A cornerstone of the plan is the formation of partnerships with industry and other national and international groups to foster regulatory acceptance and use of alternative methods.

During FY 2008, NICEATM, in conjunction with ICCVAM, convened an independent scientific peer review panel to evaluate new versions and broader applications of the murine Local Lymph Node Assay (LLNA), an alternative test method for assessing the potential for chemicals and products to induce allergic contact dermatitis. The panel reviewed the LLNA limit dose procedure, an expanded applicability domain of the LLNA including usefulness for pesticide formulations, three non-radioactive modifications to the traditional LLNA, draft ICCVAM performance standards for LLNA, and the use of the LLNA for potency determinations.

NICEATM-ICCVAM is currently working with other organizations (ECVAM, JaCVAM, and Health Canada) on an important new proposal called the International Cooperation on Alternative Test Methods (ICATM). The purpose of the ICATM is to promote enhanced and consistent international cooperation, collaboration, and communication among national validation organizations. This will ensure optimal design and conduct of validation studies, facilitate high quality independent scientific peer reviews, enhance the likelihood of harmonized recommendations by national validation organizations, leverage limited resources to achieve greater efficiency and effectiveness and avoid duplication of effort, and support the timely international adoption of alternative methods.

Table 10: NICEATM-ICCVAM Publications in FY 2008

Date	Title
February 5, 2008	The NICEATM-ICCVAM Five-Year Plan (2008-2012)
February 5, 2008	NIH Press Release: "Plan Expedites Alternatives to Animal Testing"
March 2008	"Toxicity Testing Takes Stock," *Environmental Health Perspectives*, 116:113
March 28, 2008	Report on the ICCVAM-NICEATM/ECVAM Scientific Workshop on Alternative Methods to Refine, Reduce or Replace the Mouse LD50 Assay for Botulinum Toxin Testing
May 1, 2008	ICCVAM Background Review Document: Validation Status of Five *In Vitro* Test Methods Proposed for Assessing Potential Pyrogenicity of Pharmaceuticals and Other Products
May 1, 2008	ICCVAM Test Method Evaluation Report: Validation Status of Five *In Vitro* Test Methods Proposed for Assessing Potential Pyrogenicity of Pharmaceuticals and Other Products
May 20, 2008	Independent Scientific Peer Review Panel Report - Validation Status of New Versions and Applications of the Murine Local Lymph Node Assay: A Test Method for Assessing the Allergic Contact Dermatitis Potential of Chemicals and Products
June 23, 2008	NIH Press Release: "Newly Approved Ocular Safety Methods Reduce Animal Testing"
September 2008	"Ocular Safety Assays Accepted," *Environmental Health Perspectives*, 116(9) A381

Table 11: NICEATM-ICCVAM Workshops and Peer Review Meetings in FY 2008		
Date	**Meeting**	**Topics**
February 6-7, 2008	Workshop on Acute Chemical Testing: Advancing *In Vitro* Approaches and Humane Endpoints for Systemic Toxicity Evaluations Organized and sponsored by NICEATM, ICCVAM, European Centre for the Validation of Alternative Methods (ECVAM), and the Japanese Center for the Validation of Alternative Methods (JaCVAM).	• Discussions regarding the identification of knowledge gaps in the understanding of key pathways involved in acute systemic toxicity. • Goal of determining how key *in vivo* toxicity pathway information can be collected and used to develop more predictive mechanism-based *in vitro* tests and earlier, more more humane endpoints.
March 4-6, 2008	Independent Scientific Peer Review: Validation Status of the Murine Local Lymph Node Assay (LLNA) for the Assessment of the Contact Dermatitis Potential of Chemicals and Products.	• Evaluation of modifications and new applications of the LLNA • Current and planned activities are finalizing the limit dose procedure background review document (BRD) and ICCVAM test method evaluation report, working to harmonize LLNA performance standards with ECVAM and publishing the final recommendations, requesting additional existing data for the three non-radioactive modified LLNA methods and updating those BRDs, reconvening the peer panel, and updating Organisation for Economic Cooperation and Development (OECD) Test Guideline 429, the international test guideline for the LLNA.

Table 12: Nominations or Submissions Reviewed by NICEATM-ICCVAM in FY 2008	
Test Method Nomination or Submission	**Nominator or Sponsor/Activity Status**
NTP Two-Year Toxicology and Carcinogenesis Rodent Studies	Anonymous/received October 24, 2007; presented at June, 2008 SACATM meeting.
In vitro test method for assessment of the eye irritation potential of antimicrobial cleaning products	Alternatives Testing Steering Committee: JohnsonDiversey, S.C. Johnson & Son, Inc., The Procter & Gamble Company, and The Accord Group.

Table 13 NICEATM-ICCVAM Recommendations in FY 2008	
Test Method	**ICCVAM Recommentations/Agency Status**
Alternative, Non-Animal Ocular Toxicity; Bovine Corneal Opacity and Permeability (BCOP) assay and Isolated Chicken Eye (ICE) assay.	ICCVAM recommended that the BCOP and ICE test methods can be used in a tiered testing strategy to determine ocular hazards, with specific limitations for certain chemical classes and/or physical properties. The methods should always be considered before using animals for ocular testing, and should be used where determined approporiate. These methods do not involve the use of live animals; tissues used are obtained from animals intended for food consumption. Recommendations were forwarded to Federal agencies on October 2007 and accepted April 2008. Draft test guidelines were forwarded to the OECD August 20, 2008.
In Vitro Cytotoxicity Test Methods for Estimating Starting Doses for Acute Oral Systemic Toxicity Tests using 3T3 and NHK cells.	Methods should always be considered before using animals for acute oral toxicity testing, and used where determined appropriate; can be used in a weight-of-evidence approach for determining starting doses for *in vivo* studies. Recommendations were forwarded to Federal agencies in March 2008 and endorsed by Federal agencies in September 2008.
In Vitro Test Methods for Proposed for Assessing Potential Pyrogenicity of Pharmaceuticals and Other Products	Although none of these test methods can be considered a complete replacement for the rabbit pyrogen test (RPT) for the detection of Gram-negative endotoxin, they can be considered for use to detect Gram-negative endotoxin in human parenteral drugs on a case-by-case basis, subject to validation for each specific product to demonstrate equivalence to the RPT, in accordance with applicable U.S. Federal regulations. Recommendations were forwarded to Federal agencies in November 2008, with agency responses due by April 2009.

Contact information: NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, Dr. William Stokes, Director. *niceatm@niehs.nih.gov* or NICEATM/ICCVAM website *http://iccvam.niehs.nih.gov*

Highlighted Activities

Levels of Evidence Criteria for Immuntoxicology, Reproductive Toxicology, and Developmental Toxicology Studies

The NTP describes the results of individual toxicology and carcinogenicity studies on a substance and notes the strength of evidence for conclusions regarding each study (*http://ntp.niehs.nih.gov/go/baresults*). In 2008, the NTP initiated development of specific criteria for describing the conclusions from its immunotoxicology, reproductive toxicology, and developmental toxicology studies. The draft criteria were patterned after the carcinogenicity levels of evidence criteria. The NTP convened working groups of the BSC in August and September 2008 to evaluate the utility and applicability of the three sets of draft criteria. Their reports, including proposed revisions to the criteria, were presented to the BSC in November 2008; the reports were approved and the BSC had additional discussion (*http://ntp.niehs.nih.gov/go/9741*). The NTP will consider the working group and BSC inputs and finalize the criteria for presentation at an exhibitor's session on Tuesday, March 17, 2009, at the Annual Society of Toxicology Meeting.

Contact Information: Dr. Paul Foster, *foster2@niehs.nih.gov* or Dr. Dori Germolec, *germolec@niehs.nih.gov*.

NTP/NHGRI/EPA- High-Throughput Screening, Toxicity Pathway Profiling and Biological Interpretation of Findings

A five-year memorandum of understanding (MOU), *High-Throughput Screening, Toxicity Pathway Profiling and Biological Interpretation of Findings,* was signed on February 14, 2008. With this MOU, NTP is partnering with the National Human Genome Research Institute's (NHGRI) NIH Chemical Genomics Center (NCGC) and the U.S. EPA's National Center for Computational Toxicology located within the Office of Research and Development. A *Science* article, published February, 15, 2008, authored by NHGRI Director Francis Collins, M.D., Ph.D., Assistant Administrator of EPA's Office of Research and Development George Gray, Ph.D., and NTP's John Bucher, Ph.D. describes the long-range vision for toxicity testing and assessment paradigms to meet evolving regulatory needs that form the basis for this MOU. Table 14 lists the activities included in the high throughput screening high throughput screening (HTS) initiative and the contributions from the three partners. Through this partnership it will be possible to pool resources, overcome the resource limitations of a single agency, build on existing expertise, and avoid the need to create a new administrative and support structure.

Table 14: High Throughput Activities in FY 2008

Activities	NTP	NCGC	EPA
Historical Toxicology Data	✔		✔
Experimental Toxicology	✔		✔
Ultra High-Throughput Testing		✔	
Mid- to High Throughput Systems			✔
Lower Organism Model System	✔ *C. elegans*		✔ Zebrafish
In Vitro 3-D Model Systems	✔		✔
Effect of Human/Animal Genetic Background on Toxic Effects	✔	✔	
Computational Toxicology	✔	✔	✔
Validation Experience	✔ (NICEATM-ICCVAM)	✔	✔

The partners plan to test a library of ~ 10,000 compounds that broadly characterizes and defines the chemical-biological space occupied by chemicals of toxicological concern, in quantitative HTS assays that inform on critical cellular pathways. These quantitative HTS assays are being conducted at the NCGC and data from these assays, along with full chemical characterization and assay protocol details, are being deposited into publicly accessible relational databases such as PubChem (*http://pubchem.ncbi.nlm.nih.gov/*). Secondary screens using the *C. elegans* model (*http://www.niehs.nih.gov/research/atniehs/labs/lmt/cg/index.cfm*), are under development and the tripartite collaboration between the NTP, EPA, and NCGC will establish a full spectrum of secondary and tertiary screening assays to further define and characterize activities identified in initial high throughput screens.

By the end of FY 2008, a smaller library of ~2800 compounds provided to the NCGC by the NTP and the EPA had been tested in the following assays:

- CellTiter-Glo® Luminescent Cell Viability Assay (13 cell types - 9 human, 4 rodent; also in 40 lympho blastoid cell lines from 20 sets of identical twins)
- Cytotox-ONE™Homogeneous Membrane Integrity Assay and a proteolytic release assay (both in 2 cell types)
- Caspase-Glo® Assays for caspases 3/7 (13 cell types) and 8 or 9 (6 cell types each)
- P53 signaling pathway in Hematopoietic Stem -116 cells
- Nuclear erythroid 2 p45-related factor 2/ Antioxidant Response Element signaling pathway in HepG2 cells
- Heat shock protein70 stress protein pathway
- Differential cytotoxicity in chicken lymphoblastoid cell lines deficient in different DNA repair pathways (wild-type plus 7 repair deficient clones) to detect genotoxic compounds
- 10 nuclear receptors (agonist and antagonist): androgen receptor, estrogen receptor α, bile acid-activated receptor, glucocorticoid receptor, liver X receptor β, peroxisome proliferator-activated receptor (PPAR) δ and γ, retinoid X receptor, thyroid hormone receptor β, vitamin D receptor, and retinoid-related orphan receptor α
- Human and rat pregnane X receptor reporter gene assays

Contact Information: Dr. Raymond Tice, *tice@niehs.nih.gov.* HTS website: *http://ntp.niehs.nih.gov/go/28213.*

The Phthalate Initiative

Di-(2-ethyl)hexyl phthalate (DEHP) and other phthalates have been nominated on a number of occasions to the NTP for testing. To address these nominations, the NIEHS and EPA signed The Phthalate Initiative interagency agreement in June 2008, which continues from August 2008 to June 2009. Many aspects of The Phthalate Initiative fall under nominations previously approved by the BSC for the study of peroxisome proliferators (initiated in the 1990s), the nomination of DEHP by FDA in 2004, and the critical data need highlighted in the NTP-CERHR Monograph on DEHP issued in 2006. These studies will elucidate the developmental ontogeny of PPARα in the rat and relationship to DEHP cancer (and other developmental toxicity) outcomes. In addition, the studies will provide the critical data to undertake mixture studies using various model approaches, to inform on potential cumulative and

aggregate cancer and developmental toxicity risk. Recent data have indicated that because of similar modes of action *in utero*, phthalate esters show dose-addition when administered in combination, therefore, it would be appropriate to consider cumulative risk for the class, since human subjects (including fetuses) are typically exposed to multiple phthalates.

The initiative has two specific aims:

(1) Undertake an ontogeny study of PPARα in the rat to determine when the receptor is first expressed in target tissues. This will test the hypothesis that PPARα is developmentally regulated in the rat and unlikely to contribute to toxicity initiated *in utero* after exposure to DEHP.

(2) Undertake perinatal phthalate mixture studies. This will test the hypothesis that exposures to mixtures of phthalates, based on their individual potencies, would result in dose addition for cancer (and potentially other) outcomes.

These data would guide the needs for individual perinatal bioassays and mixture work to support NTP DEHP studies. Since the question of cumulative risk for phthalates has been the subject of a recent National Academy of Sciencies committee, this overall approach is seen as providing extra impetus to fill these data gaps.

Contact Information: Dr. Paul Foster, *foster2@niehs.nih.gov.*

Cellular Phone Radiation Emissions

The single most costly and technically challenging study ever undertaken by the NTP is a multi-year study to address the potential health-related adverse effects of the radiation emitted by cellular phones and cell towers. The overall goal of these studies is to determine the potential toxic and/or carcinogenic effects of exposure to cellular phone radiofrequency emissions in laboratory animals. Exposure chambers were constructed in Switzerland and transported to Chicago, and they are undergoing final performance evaluations prior to starting rodent exposure studies. Thermal pilot studies and prechronic studies are slated to begin in 2009 and chronic studies in 2010. The estimated cost of these studies is approximately 23 million dollars. The Federal Communication Commission and other stakeholders will use this information to establish guidelines for protecting against potential adverse health effects of chronic exposure to these emissions.

Contact Information: Dr. Michael Wyde, *wyde@niehs.nih.gov.*

Nanotechnology Safety Initiative

Nanoscale materials are materials that encompass a size range of approximately 1nm to several hundred nanometers. While they are already appearing in commerce as industrial and consumer products and as novel drug delivery formulations, there is little research focus on the potential toxicity of manufactured nanoscale materials. In addition, the unique and diverse physicochemical properties of nanoscale materials suggest that toxicological properties may differ from materials of similar composition but larger size.

The NTP is currently engaged in a broad-based research program to address potential human health hazards associated with the manufacture and use of nanoscale materials. This initiative is driven by the current and anticipated future research and development focus on nanotechnology.

Ongoing research activities are initially focusing on several classes of materials namely:

- nanoscale metal oxide powders (TiO_2)
- cadmium-based fluorescent nanocrystalline semiconductors (quantum dots) carbon fullerenes
- carbon nanotubes
- metal-based nanoparticles (nanosilver and nanogold)

This research is carried out by developing and using a suite of analytical approaches to evaluate and characterize the physiochemical properties of nanoscale materials in their raw form and as formulated when given to animals or exposed to cells in culture. In addition, NTP is conducting animal toxicity studies of varying durations with specific nanomaterials using routes of administration that mimic possible human exposure, including inhalation routes of exposure. These studies will include evaluations of the absorption and handling of the materials by rodents. We are also employing *in vitro* models to evaluate the biological and toxicological effects of nanoscale materials.

The ultimate goal of this research program is to evaluate the toxicological properties of several nanoscale materials classes that represent a cross-section of composition, size, surface coatings, and physicochemical properties, and use these to investigate fundamental questions concerning if and how nanoscale materials interact with biological systems and potentially cause adverse effects in humans.

Contact information: Dr. Nigel Walker, *walker3@niehs.nih.gov.*

DNA-based Systems

DNA-based systems hold promise for new gene replacement therapies, but currently they are experimental. By their nature, DNA-based therapies pose the risk of unintended gene interactions and disruption of cell functions. Several DNA-based therapies exist, which use viral vectors, bacterial plasmids, non-coding RNA or synthetic nucleotides. The NTP is collaborating with the FDA to examine insertional mutagenesis of retroviral and lentiviral vectors in hematopoietic stem cells. Vectors are used to introduce, and integrate into the genome, theraputic genes into the population of stem cells. These serve as a renewable source of cells expressing theraputic gene products.

NTP is also collaborating with the NIH Institute for Dental and Craniofacial Research to evaluate the safety of using the protein-secreting ability of salivary glands, transduced with different vector-transgene combinations, to express and secrete transgene-encoded therapeutic proteins into serum for treatment of single-protein deficiency diseases. There is relatively easy access to the salivary glands. These glands are encapsulated, which potentially limits the systemic dissemination of gene transfer vectors. To date, three studies have been completed using recombinant adenoviral vectors delivered to rodent salivary glands.

Contact Information: Dr. Richard Irwin, *irwin@niehs.nih.gov.*

Mold Studies at NTP

Natural disasters such as hurricanes, new construction methods, and better sealing and insulation in buildings have all led to an increase in indoor mold levels. Exposure to elevated levels of indoor mold has been associated with respiratory, neurologic, and gastrointestinal changes. Molds were nominated for study and NTP is designing studies to evaluate the health effects of commonly found mold (*Aspergillus*, *Penicillium*, and *Stachybotrys*) to better understand how exposure to mold may cause disease.

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Aspergillis Mold

Specific aims of the NTP studies are: (1) assess organ system toxicity following inhalation exposure to molds, (2) evaluate the available biomarkers of exposure and effect (both general and specific for the organisms to be studied), and (3) evaluate the contribution of different organisms to overall health effects by studying individual isolates as well as mixtures. Subchronic studies in rodents using inhalation as the route of exposure will be used. Two test mixtures that attempt to simulate real-life exposures scenarios will be used (from a water-damaged building in New Orleans and a building with reported "sick-building syndrome").

Contact Information:, Dr. Dori Germolec, *germolec@niehs.nih.gov.*

Herbal Medicines and Dietary Supplements

Herbals and dietary supplements are a major focus area for the NTP. The NTP is currently studying 16 of the 25 top-selling herbal and dietary supplements. Table 15 includes a listing of the compounds for which studies are completed, ongoing, or planned. The compounds can be loosely classified as "multipurpose" (*Aloe vera*, *Echinacea*, gum guggul, kava, milk thistle, pulegone/pennyroyal, and senna laxative), "women's health" (black cohosh, gum guggul, dong quai), "cancer chemopreventives" (green tea extract, indole carbinol, resveratrol, melatonin), "anti-aging" (ginseng, glucosamine/chondroitin sulfate, *Ginko bilobo*, vincamine), and weight loss/sports aids (*Usnea* lichen/usinic acid, chitosan, *Garcinia cambogia*, bitter orange extract, androstenedione).

Table 15: Herbal Ingredients and Dietary Supplements

Substance [CASRN]	Project Leader	Use and/or Rationale
Aloe vera (oral) [8001-97-6]	Boudreau	*Aloe vera* has widespread oral and dermal exposure in humans and lack of toxicity information; there is a suspicion of carcinogenicity. The 1998 FDA Special Nutritional Adverse Event Monitoring System lists Aloe vera exposure associated with numerous adverse effects in humans.
Androstenedione [63-05-8]	Blystone	There is a potential for abuse by athletes, bodybuilders, and young adults as a steroidal precursor to testosterone. Little scientific data are available on chronic toxicity. Several compounds structurally related to androstenedione inhibit aromatase and are used to treat estrogen-dependent breast cancer in postmenopausal women.
Arbutin [497-76-7]	Chan	Consumer exposure occurs through food, cosmetics, and dietary supplements. There is a lack of adequate toxicological data and suspicion of toxicity based on chemical structure.

Substance [CASRN]	Project Leader	Use and/or Rationale
Bitter orange extract	Hansen	Consumer exposure is through increasing dietary supplement use (the most common replacement for ephedra, banned from use by the FDA in 2003, in dietary supplements for weight loss). There is suspicion of toxicity and a lack of adequate toxicity data.
Black cohosh [84776-26-1]	Stout	Black cohosh is a dietary supplement used for the treatment of menstrual and menopausal symptoms in women. It appears to bind to estrogen receptors and causes luteinizing hormone suppression. There is a lack of chronic studies in humans or animals.
Chitosan [9012-76-4]	Chhabra	Chitosan is a popular dietary supplement used for weight loss. Several subacute studies in animals show that it has hypercholesterolemic properties and may influence weight gain; it may also cause vitamin and mineral deficiencies. There is a potential for Vitamin E depletion and osteoporosis from ingestion.
Chondroitin sulfate/ Glucosamine [9007-28-7]	Leakey	It is a dietary supplement that is widely used alone and in combination with glucosamine to alleviate pain and inflammation from osteoarthritis. No data are available on the possible adverse or toxic effects from long-term exposure.
Dong quai *(Angelica sinensis root)* and extract	Wyde	Don quai has widespread use as a dietary supplement and in Chinese herbal medicine as an antispasmodic or blood purifier and for reduction of pain, dilation of blood vessels, and stimulation, as well as relaxation of uterine muscles. There is suspicion of toxicity based on estrogenic activity and chemical structure and there is a lack of adequate toxicity data.
Echinacea purpurea, extract [90028-20-9]	Irwin	Echinacea is the most popular herbal supplement in the US, creating widespread human exposure. It is used to stimulate the immune system and there is a lack of scientific literature supporting its safety or efficacy.
Epigallocatechin (Green tea extract) [989-51-5]	Chan	Epigallocatechin is a potential cancer chemopreventive agent. It is an antioxidant that is thought to prevent tumorigenesis by protecting cellular components from oxidative damage via free radical scavenging. It is a major component of the polyphenolic fraction of green tea. It requires evaluation with regard to its toxicity.
Garcinia cambogia extract [90045-23-1]	Wyde	*Garcinia cambogia* is marketed as an ephedra-free diet aid and there is consumer exposure through increasing dietary supplement use. There is a lack of adequate toxicological data.
Ginkgo biloba extract [90045-36-3]	Chan	There is potential for widespread exposure through use as a dietary supplement for “improving brain functioning” or “promoting radical scavenging activity.” *Ginkgo biloba* clearly demonstrates biological activity and can be consumed in rather large doses for an extended period of time. Some ingredients are known mutagens or suspected carcinogens.
Ginseng [50647-08-0]	Chan	Gensing has widespread use as a dietary supplement. There is a possibility that ginseng and ginsenosides may have anticarcinogenic activity. There is a lack of toxicity information.
Glucosamine [3416-24-8]	Leakey	Chondroitin sulfate is a widely used dietary supplement, both alone and in combination with glucosamine to alleviate pain and inflammation from osteoarthritis. There are no data on the possible adverse or toxic effects from long-term exposure.
Goldenseal root powder	Dunnick	Berberine, a constituent of goldenseal, has showed some activity against fungal infections, candida, yeast, parasites, and bacterial/viral infections. The nomination of goldenseal and two of its constituent alkaloids is based on the potential for human exposure and the lack of chronic or carcinogenicity data.
Gum guggul extract	Wyde	Gum guggul has expanding use as a dietary supplement and has demonstrated biological effects on lipid metabolism, thyroid hormone homeostatsis, female reproductive tissues, endogenous nuclear hormone receptors and the potential for serious drug interactions. There is a lack of available information to adequately assess safe use in humans.

Substance [CASRN]	Project Leader	Use and/or Rationale
Indole-3-carbinol [700-06-1]	Wyde	Indole-3-carbinol is marketed as a dietary supplement with projected rapid growth in sales. It is found in Brassica vegetables and is under review at NCI as a chemopreventive agent for breast cancer. Substantial evidence exists that indole-3-carbinol can reduce the risk of cancers induced by several carcinogens when administered to animals. However, it also induces cytochrome P450 1A1 through the Ah receptor, a process often associated with toxicity.
Kava kava extract [9000-3-8]	Chan	Kava kava is a dietary supplement with widespread use; it has been promoted as a substitute for ritilin in children. There is insufficient toxicity data available. NCI recommended testing kava extract standardized to 30% kavalactones
Melatonin [73-31-4]	Travlos	Melatonin, a hormone produced by the pineal gland, has become very popular as an over-the-counter hormone supplement as well as being used as a chemotherapeutic agent in cancer. There is a lack of toxicity information and a suggestion that melatonin may have the potential to cause ocular toxicity.
Milk thistle extract [84604-20-6]	Dunnick	Milk thistle extract is a popular dietary supplement thought to have beneficial effects on the liver; however, there is limited information on its safety. Metabolism studies are needed to resolve questions regarding bioavailability of orally administered milk thistle extract.
Pulegone (Pennyroyal) [89-82-7]	Chan	The nomination of pulegone and menthofuran for testing is based on the potential for human exposure and the absence of carcinogenicity data. Pulegone is a major constituent of pennyroyal and menthofuran is one of the metabolites of pulegone.
trans-Resveratrol [501-36-0]	Germolec	*trans*-Resveratrol is found in grapes and wine and is currently marketed in pure or extract form as a dietary supplement. It has numerous reported beneficial effects but toxicity is poorly characterized.
Retinyl palmitate	Howard	Retinyl palmitate was nominated for phototoxicity and photocarcinogenicity testing based on the increasingly widespread use of this compound in cosmetic retail products for use on sun-exposed skin and the need to investigate the biochemical and histological cutaneous alterations elicited by retinyl palmitate and the association between topical application of retinoids and enhancement of photocarcinogenesis.
Senna (powdered) [8013-11-4]	Dunnick	The safety of laxatives is currently being reassessed by the FDA as a result of the testing of phenolphthalein for carcinogenicity in rodents. Senna has been reported as positive in the Ames test and a preliminary 2-year rat study showed an increase in lymph node hyperplasia. The Center for Drug Evaluation and Research is requesting a p53 hemizygous study to compliment a 2-year rat study sponsored by the manufacturer.
Silymarin [65666-07-1]	Dunnick	See milk thistle extract.
Silybin [22888-70-6]	Dunnick	See milk thistle extract.
α/ß-beta Thujone mixture [546-80-5] [471-15-8]		Thujone was identified through a review of direct food additives given "GRAS" status by the FDA. It has known toxicity that has caused it to be banned from some products. Twenty-four direct food additives in the FDA Priority-Based Assessment of Food Additives contain thujone. There is a potential for widespread consumer and worker exposure.
Usnea barbata, extract [84696-53-7]	Leakey	*Usnea barbata* is used as dietary supplements for weight loss.
Usnic acid and *Usnea* herb [125-46-2]	Leakey	There is widespread use in dietary supplements and personal care products. There is a lack of adequate toxicological data and numerous human adverse event reports.
Vincamine [1617-90-9]	Chan	Consumer exposure to Vincamine occurs through dietary supplement use. There is a suspicion of toxicity and a lack of adequate toxicological data.

[1]*Testing Status and study results for completed studies can be found at http://ntp.niehs.nih.gov/ select "Testing Status of Agents at NTP" and "Study Results and Research Projects."*

Use of NTP Products by Other Agencies

Federal and state regulatory agencies use NTP study data and recommendations in considering the need for regulation and testing of specific chemicals to protect human health. Table 16 lists the NTP data and recommendations utilized in FY 2008.

Table 16: Federal and State Regulatory Agencies use of NTP Study Data or Recommendations in FY 2008

Compound, Standard/Title and Agency	NTP Information Cited
Decabromodiphenyl ether (BDE-209)/ EPA-Integrated Risk Information System (IRIS)	TR-309 – toxicology and carcinogenesis studies of decabromodiphenyl oxide in F344/N rats and B6C3F1 mice (feed studies).
Propionaldehyde [123-38-6] /EPA-IRIS	TR-472 – toxicology and carcinogenesis studies of Isobutyraldehyde (CAS 78-84-2) in F344/N Rats and B6C3F1 Mice.
Anthraquinone [84-65-1]/ California Office of Environmental Health	TR-494 – toxicology and carcinogenesis studies of Anthraquinone in F344/N Rats and B6C3F1 Mice (Feed Studies). Also listed in the 11th Report on Carcinogens (2004) as reasonably anticipated to be a human carcinogen.
Dibromoacetic acid [631-64-1]/ California Office of Environmental Health	TR-537 – toxicology and carcinogenesis studies of Dibromoacetic Acid in F344/N Rats and B6C3F1 Mice (drinking water studies).
Sixty-Second Report of the TSCA Interagency Testing Committee (ITC) to the Administrator of the EPA/EPA	The ITC is removing tungsten oxide (WO3, tungsten trioxide) because of the voluntary information provided by the International Tungsten Industry Association and their cooperation in a NIOSH/NTP research program to address exposure and toxicity data needs. The ITC is retaining tungstate, disodium, dihydrate, sodium tungstate, dihydrate on the Priority Testing List because of ongoing discussions with the International Tungsten Industry Association.
Control of Emissions of Air Pollution from Locomotive Engines and Marine Compression-Ignition Engines Less than 30 Liters per Cylinder/EPA	In the 11th RoC, NTP listed naphthalene as reasonably anticipated to be a human carcinogen; benzene as a known human carcinogen; 1,3-butadiene as a know human carcinogen; and acetaldehyde as reasonably anticipated to be a human carcinogen.
Dichlorvos; Order Denying Natural Resources Defense Council Objections and Requests for Hearing	TR-342 – toxicology and carcinogenesis studies with rats and mice, male and female reproductive organs (prostate, testes, epididymis, ovaries, uterus) were examined and no changes attributable to dichlorvos were found.

Nomination, Selection, Evaluation, and Review

Nominations for Study

The NTP maintains a balanced research and testing program that provides data addressing a wide variety of issues important to public health. The NTP actively seeks to identify and select for study chemicals and other substances for which sufficient information is not available to adequately evaluate potential human health hazards. The NTP accomplishes this goal through a formal open nomination and selection process. Substances considered appropriate for study generally fall into two broad yet overlapping categories:

1. Substances judged to have high concern as a possible public health hazard based on the extent of human exposure and/or suspicion of toxicity.
2. Substances for which toxicological data gaps exist and additional studies would aid in assessing potential human health risks, e.g. by facilitating cross-species extrapolation or evaluating dose-response relationships.

Input is also solicited regarding the nomination of studies that permit the testing of hypotheses to enhance the predictive ability of future NTP studies, address mechanisms of toxicity, or fill significant gaps in the

knowledge of the toxicity of classes of chemical, biological, or physical substances. Increased efforts continue to be focused on:

- Improving the quality of the nominations of chemicals, environmental agents, or issues for study so that public health and regulatory needs are addressed.
- Broadening the base and diversity of nominating organizations and individuals.
- Increasing nominations for studying non-cancer toxicological endpoints.

The nomination process is open to the public. The NTP routinely solicits nominations at conferences and workshops; through the NTP newsletter, Federal Register notices, and NTP homepage (http://ntp.niehs.nih.gov), and from interested individuals and groups. In addition, the NCI, FDA, NIOSH, and NIEHS routinely select and forward nominations to the NTP. The NTP also reviews environmental occurrence and human exposure databases and scientific literature reports to identify substances of potential interest.

Contact Information: Office of Nomination and Selection, Dr. Scott Masten, *masten@niehs.nih.gov.*
Nomination website: *http://ntp.niehs.nih.gov/* select "Nominations to the Testing Program."

Review and Selection Process

The review and selection of substances and issues nominated for study is a multi-step process (see figure 5 and *http://ntp.niehs.nih.gov/go/156*). A broad range of concerns are addressed during this process through the participation of representatives from the NIEHS, other Federal agencies, the NTP Board of Scientific Counselors (see page 6), the NTP Executive Committee (see page 10), and the public. This multi-step evaluative process provides the NTP with direction and guidance to ensure that its testing program addresses toxicological concerns relative to all areas of public health, and furthermore, that there is balance among the types of substances selected for study (e.g., industrial chemicals, consumer products, therapeutic agents). Figure 5 summarizes the study nomination review process and Table 17 lists the nominations reviewed in FY 2008.

Fig. 5: NTP Study Nomination Review Process

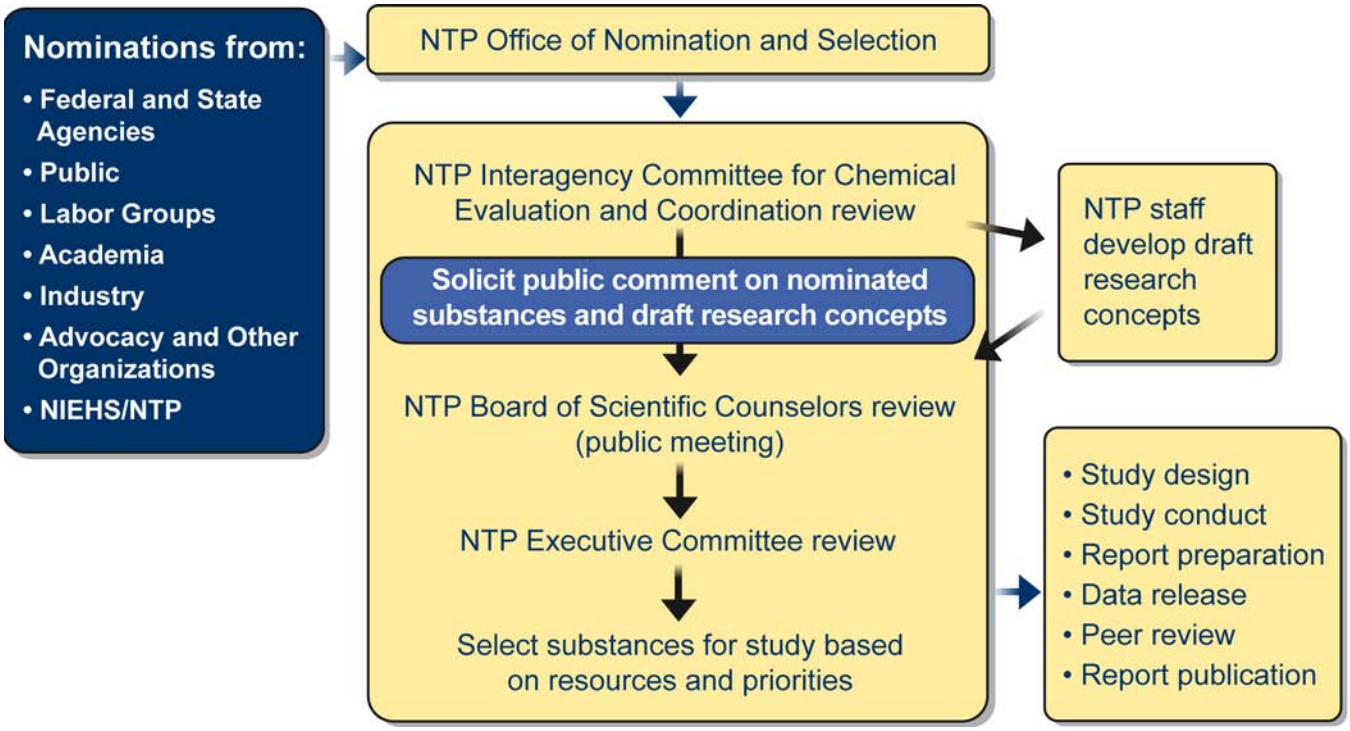


Table 17: Nominations Reviewed in FY 2008

Substance [CASRN]	Nominator	Nomination Rationale	Study Recommendation
Bisphenol AF [1478-61-1]	NIEHS	Moderate production and use in polymer synthesis; short-term studies suggest potential for endocrine disruption and adverse reproductive effects; lack of adequate toxicity data.	Comprehensive toxicological characterization
Dimethylamine borane [74-94-2]	NIOSH	Possible contact sensitizer and systemic toxicant but insufficient evidence as determined by the NIOSH Dermal Subject Matter Expert Workgroup.	• Dermal absorption studies • Skin sensitization studies • Subchronic dermal toxicity studies with neurotoxicity and behavioral assessments
Dimorpholinodiethyl ether [6425-39-4]	NCI	High production volume; potential worker exposures; lack of adequate toxicological data; suspicion of toxicity based on structure.	• Initial toxicological characterization • Studies to assess the potential for nitrosation
Ethylene glycol 2-ethylhexyl ether [1559-35-9]	NIEHS	High production volume; potential worker exposures; suspicion of toxicity based on chemical structure; lack of adequate toxicity data.	Reproductive and developmental toxicity studies
2-Ethylhexyl *p*-methoxycinnamate [5466-77-3]	NCI	High production volume; widespread consumer exposure as a common sunscreen active ingredient; reported estrogenic and reproductive effects.	• Comprehensive toxicological characterization including carcinogenicity and developmental toxicity studies • Characterization of photodecomposition products
Hydroxyurea [127-07-1]	NIEHS and private individual	Long term safety concern when used as therapy for sickle cell anemia; NTP CERHR Expert Panel identified a critical data need for multi-generational experimental animal studies to assess the long-term effects of prenatal and postnatal exposures on postnatal development including developmental neurotoxicity, reproductive function, and carcinogenicity.	No experimental animal toxicity studies at this time; human studies currently being considered by the NIH and other federal agencies may address outstanding safety concerns.
L-ß-Methylaminoalanine [15920-93-1]	NIEHS	Natural product of cyanobacteria with localized and potentially widespread environmental occurrence; suspected risk factor for neurological disease(s); lack of adequate toxicity data.	• Absorption, distribution, metabolism, and elimination studies • Neurotoxicity studies • Biomolecular screening studies
Triclosan [3380-34-5]	FDA and private individual	Widespread use in consumer products; frequent and long-term exposure for all age groups; lack of adequate toxicity data for dermal exposures.	• Carcinogenicity studies via dermal administration • Phototoxicity studies • Reproductive toxicity studies
4,7,10-Trioxatridecane-1,13-diamine [4246-51-9]		High production volume; potential worker exposures; lack of adequate toxicological data; acutely toxic.	• Biomolecular screening studies • Genotoxicity studies
Vanadium, tetravalent and pentavalent forms	NIEHS, EPA	Widespread occurrence as drinking water contaminant and use as a dietary supplement; EPA Drinking Water Contaminant Candidate List research need; pentavalent form carcinogenic via inhalation route; inadequate data to assess risk of oral exposures.	• Comprehensive toxicological characterization • Chronic toxicity and carcinogenicity studies via oral route • Multigeneration reproductive toxicity studies

Evaluation

In carrying out its mission, the NTP provides toxicological evaluations on substances of public health concern. The NTP can initiate bioassays to characterize potential carcinogenicity of only a small fraction of the thousands of substances for which there is little or no information. Many more substances are also studied to assess a variety of non-cancer health-related effects including, but not limited to, reproductive and developmental toxicities, immunotoxicity, neurotoxicity, and genotoxicity. Other biological parameters are often assessed such as quantifying the disposition and excretion of substances, identifying and correlating biochemical markers with exposure and metabolism, and examining genetic polymorphisms in human drug metabolizing enzymes to understand the susceptibility of individuals and populations to xenobiotic-induced toxicity.

An NIEHS/NTP project review committee reviews and evaluates a study's project plan (e.g., design, methods, hypothesis, etc.). The toxicological evaluation for carcinogenicity is generally conducted through repeated administration of a substance to groups of laboratory animals for variable periods of time up to two years. Many short-term studies are designed to provide dose-setting information for chronic exposure studies and address specific deficiencies in the toxicology database. The adverse health effects from short- or long-term exposures of different dose levels of the substance are evaluated clinically, by histopathology, and by a variety of toxicology end points through comparison with groups of animals not administered the substance. Many substances are also studied using protocols specifically designed to address issues pertaining to the mechanism by which the substance causes a particular toxic outcome(s). The NTP has specific requirements for the testing laboratories to comply with the Animal Welfare Act of 1966 and adhere to the principles enunciated in the "Guide for the Care and Use of Laboratory Animals" (NRC, 1996). General information about the objectives and procedures of NTP study protocols is available on the NTP website (*http://ntp.niehs.nih.gov/* select "Descriptions of NTP Study Types"). Current testing status can be found at *http://ntp.niehs.nih.gov/* select "Testing Status of Agents at NTP."

The NTP carries out toxicology and carcinogenesis testing through two primary mechanisms: laboratory studies conducted in contract laboratories (See table 18) and studies conducted via interagency agreements at federal agencies (see page 87). In addition to toxicology research of compounds and exposures, the NTP supports the development of new techniques and methods for improving the ability to identify and assess potential environmental toxicants and the development and validation of novel and alternative testing methods that will reduce, replace, or refine animal use. The NTP also supports development of improved statistical methods for designing and evaluating the results of toxicology studies.

Table 18: NTP Contracts that Support NTP Testing Activities:

Description	Contractor
ADME Chemical Disposition in Mammals	Lovelace Biomed and Env Research
ADME Chemical Disposition in Mammals	Research Triangle Institute
Cell Phone Radio Frequency	IIT Research Institute
Central Data Mgt and Information Services	Z-Tech Corporation
Chemistry Support Services	Battelle Memorial Institute
Chemistry Support Services	Midwest Research Institute
Chemistry Support Services	Research Triangle Institute
Env and Theraputic Agents to Induce Immuntox	Virginia Commonwealth Univ.
Genetic Toxicity in Bacteria and Rodents	Integrated Lab Systems
Literature Search and Summary Report	Integrated Lab Systems
Molecular Oncology and Toxicology Support	Integrated Lab Systems

Description	Contractor
NIEHS Archives and Specimen Repository	Experimental Pathology Labs
NTP Statistical and Computer Support	Constella Group
NTP Technical Reports Preparation Services	Biotechnical Services, Inc.
Pathology Support	Charles River
Pathology Support	Integrated Lab Systems
Pathology Support	Experimental Pathology Labs
QA Support for Audits and Inspections	Dynamac Corporation
Reproductive Assessments in Rodents	Research Triangle Institute
Research on Inhalation Toxicology	Alion Science and Technology
Toxicological Potential of Selected Chemicals	Battelle Memorial Northwest
Toxicological Potential of Selected Chemicals	Battelle Memorial Columbus
Toxicological Potential of Selected Chemicals	Southern Research Institute

Review and Dissemination

The results of toxicology and carcinogenesis studies undergo rigorous peer review and are published in several NTP report series:

- Technical Reports (TR). This series presents the results of long-term, generally 2-year, toxicology and carcinogenicity studies, typically conduced in two rodent species, rats and mice. Results of genetic toxicology,chemical disposition, and toxicokinetic studies are often included in TRs. The Technical Reports Review Subcommittee of the NTP BSC (see Advisory Boards and Committees, page 6) evaluates TRs in an open, public meeting.
- NTP Toxicity Reports (TOX). TOX reports are prepared for studies where the substance exposure period is short-term, generally up to 13-weeks. TOX reports are typically peer-reviewed through letter review.
- Genetically Modified Models Reports (GMM). NTP initiated the GMM report series in May 2003. This report series presents the results of substances evaluated by NTP in transgenic mouse strains (e.g., p53+/-heterozygous and Tg.AC). The Technical Reports Review Subcommittee of the NTP BSC (see Advisory Boards and Committees, page 6) evaluates GMM reports in an open, public meeting.

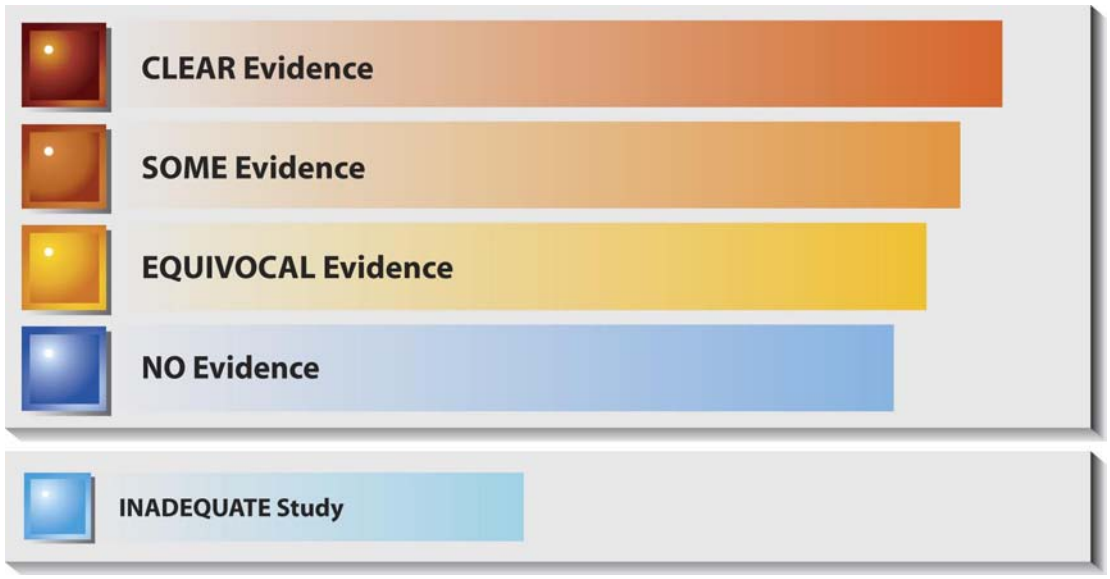
Abstracts of the TR, TOX, and GMM series are posted on the NTP website and PDF files of completed reports are available free-of-charge at the NTP website (*http://ntp.niehs.nih.gov/* select “NTP Study Reports”). TR, TOX, and GMM report series are also catalogued in PubMed. Study summaries for other types of studies, such as immunotoxicity, developmental, and reproductive studies, are also available at “NTP Study Reports.” With the finalization of the new criteria for immunotoxicity, developmental, and reproductive studies the NTP will be publishing these studies as technical reports. All types of NTP studies may also be published in peer-reviewed scientific journals.

Chronic Toxicity/Carcinogenicity Studies

In the area of general toxicology assessments, the scope and types of studies performed are dictated to a large degree by the data needs for the specific substance nominated for study. General toxicology studies usually fall into two categories: subchronic or prechronic studies and 2-year chronic toxicology and carcinogenicity studies. Two-year studies in rodents remain the primary laboratory method by which chemicals or physical agents are identified as having the potential to be hazardous to man.

The chronic toxicology and carcinogenicity studies in conventional rodent models generally employ both genders of rats (Fischer 344/N, Harlan Sprague-Dawley, or Wistar Han) and mice (B6C3F1 hybrid) with three exposure levels plus untreated controls in groups of 50 animals for two years; other models, e.g., genetically modified mouse are used as needed. If adequate data exist in the literature for one rodent species, then typically only the remaining species is studied. The NTP interfaces its testing with regulatory agencies and the private sector in order to minimize duplication of effort. Studies ongoing, initiated, completed, and published in FY 2008 are listed in Tables 19, 20, 21 and 22.

NTP describes the results of individual experiments on a chemical agent and notes the strength of evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans.



Five categories of evidence of carcinogenic activity criteria (available at *http://ntp.niehs.nih.gov/go/baresults*) are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results ("*Clear Evidence*" and "*Some Evidence*"); one category for uncertain findings ("*Equivocal Evidence*"); one category for no observable effects ("*No Evidence*"); and one category for experiments that because of major flaws cannot be evaluated ("*Inadequate Study*"). These conclusion statements are peer-reviewed by the NTP TRRS.

Table 19: Ongoing Chronic Toxicity/Carcinogenicity Studies During FY 2008					
Chemical	**[CASRN]**	**Species/Strain**	**Route**	**Study Length**	**Project Leader**
Acrylamide	[79-06-1]	Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-) Rats: F344 (NCTR)	Dosed-water	2 years	Beland
Aloe vera whole leaf extract (native)		Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-) Rats: F344 (NCTR)	Dosed-water	2 years	Boudreau
Androstenedione	[63-05-8]	Mice: B6C3F1 Rats: F344/N	Gavage	2 years	Blystone
Antimony trioxide	[1309-64-4]	Mice: B6C3F1 Rats: Wistar Han	Inhalation	2 years	Stout
3'-Azido-3'-deoxythymidine (AZT)	[30516-87-1]	Mice: B6C3F1 Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Gavage	2 years	Beland
AZT/Drug Combinations Transplacental/ Neonatal Study		Mice: B6C3F1	Gavage	2 years	Leakey
AZT/Drug Combinations Transplacental Carcinogenesis Study		Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	*In Utero*	2 years	Leakey
1-Bromopropane	[106-94-5]	Mice: B6C3F1 Rats: F344/N	Inhalation	2 years	Morgan
bis (2-Chloroethoxy)methane	[111-91-1]	Mice: B6C3F1 Rats: F344/N	Topical application	2 years	Dunnick
Cobalt	[7440-48-4]	Mice: B6C3F1 Rats: F344/NTAC	Inhalation	2 years	Hooth
Diethylamine	[109-89-7]	Mice: B6C3F1 Rats: F344/N	Inhalation	2 years	Morgan
N,N-Dimethyl-*p*-toluidine	[99-97-8]	Mice: B6C3F1 Rats: F344/N	Gavage	2 years	Dunnick
Ginkgo biloba extract	[90045-36-6]	Mice: B6C3F1 Rats: F344/N	Gavage	2 years	Chan
Ginseng	[50647-08-0]	Mice: B6C3F1 Rats: F344/N	Gavage	2 years	Chan
Glycidamide	[5694-00-8]	Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-) Rats: F344 (NCTR)	Dosed-water	2 years	Beland
Goldenseal root powder	[50647-08-0]	Mice: B6C3F1 Rats: F344/N	Dosed-feed	2 years	Dunnick
Green tea extract		Mice: B6C3F1 Rats: Wistar Han	Gavage	2 years	Chan
Indole-3-carbinol	[700-06-1]	Mice: B6C3F1 Rats: Harlan Sprague-Dawley	Gavage	2 years	Wyde
Kava kava extract	[9000-38-8]	Mice: B6C3F1 Rats: F344/N	Dosed-feed	2 years	Chan
Metal working fluids (CIMSTAR 3800)		Mice: B6C3F1 Rats: Wistar Han	Inhalation	2 years	Kirby

Chemical	[CASRN]	Species/Strain	Route	Study Length	Project Leader
Methyl trans-styryl ketone	[1896-62-4]	Mice: B6C3F1 Rats: F344/N	Topical application	2 years	Cunningham
Milk thistle extract	[84604-20-6]	Mice: B6C3F1 Rats: F344/N	Dosed-feed	2 years	Dunnick
beta-Myrcene	[123-35-3]	Mice: B6C3F1 Rats: F344/N	Gavage	2 years	Chan
Pentabromodiphenyl oxide (technical) (DE 71)	[32534-81-9]	Mice: B6C3F1 Rats: Wistar Han	Gavage	2 years	Dunnick
beta-Picoline	[108-99-6]	Mice: B6C3F1 Rats: F344/N	Dosed-water	2 years	Wyde
Pulegone	[89-82-7]	Mice: B6C3F1 Rats: F344/N	Gavage	2 years	Auerbach
Pyrogallol	[87-66-1]	Mice: B6C3F1 Rats: F344/N	Topical application	2 years	Wyde
All-trans-retinyl palmitate	[79-81-2]	Mice: SKH-1 Hairless	Topical application	2 years	Boudreau
Styrene-acrylonitrile trimer	[84604-20-6]	Rats: F344/N	Dosed-feed	2 years	Chhabra
Polychlorinated biphenyl 118 (toxic equivalency factor evaluation)	[31508-00-6]	Rats: Harlan Sprague-Dawley	Gavage	2 years	Walker
Tetrabromobisphenol A	[79-94-7]	Mice: B6C3F1, Rats: F344/NTAC Rats: Wistar Han	Gavage	2 years	Dunnick
3,3',4,4'-Tetrachloroazobenzene	[14047-09-7]	Mice: B6C3F1 Rats: Harlan Sprague-Dawley	Gavage	2 years	Hooth
Tetralin	[119-64-2]	Mice: B6C3F1 Rats: F344/N	Inhalation	2 years	Chan
alpha/beta Thujone mixture	[50647-08-0]	Mice: B6C3F1 Rats: F344/N	Gavage	2 years	Hooth
Trimethylolpropane triacrylate	[15625-89-5]	Mice: SKH-1 Hairless	Topical application	2 years	Chhabra
Vinylidene chloride	[75-35-4]	Mice: B6C3F1 Rats: F344/N	Inhalation	2 years	Wyde
Water disinfection byproducts (Bromodichloroacetic acid)	[79-94-7]	Mice: B6C3F1 Rats: F344/NTAC	Dosed-water	2 years	Dunnick

**Indicates study conducted using genetically-modified model*

Table 20: Chronic Toxicity/Carcinogenicity Studies Initiated FY 2008

Chemical	[CASRN]	Species/Strain	Route	Study Length	Project Leader
Antimony trioxide	[1309-64-4]	Rats: Wistar Han	Inhalation	2 years	Stout
Metal working fluids (Trim VX)		Mice: B6C3F1 Rats: Wistar Han	Inhalation	2 years	Kirby
Pentabromodiphenyl oxide (technical) (DE 71)	[32534-81-9]	Mice: B6C3F1 Rats: Wistar Han	Gavage	2 years	Dunnick
Perfluorooctanoic acid (PFOA)	[335-67-1]	Rats: Harlan Sprague Dawley	Dosed-feed	2 years	Blystone

Table 21: Technical Reports Completed During FY 2008

Chemical/Exposure–Study Type	[CASRN]	Technical Report Number	Use
Aloe Vera Photococarcinogenesis studies: - Aloe-emodin - Aloe vera charcoal filtered whole leaf extract - Aloe vera gel - Aloe vera whole leaf extract (native)	 [481-72-1] [8001-97-6]	TR-553	Aloe is a natural product used in many health care products and cosmetics.
Bromochloroacetic acid	[5589-96-8]	TR-549	EPA water chemical; byproduct of water chlorination
Chromium picolinate monohydrate	[27882-76-4]	TR-556	Used as a dietary supplement for losing weight
Dibromoacetonitrile	[3252-43-5]	TR-544	Intermediate in organic synthesis
1,2-Dibromo-2,4-dicyanobutane	[35691-65-7]	TR-555	As a preservative in paints, emulsions, dispersed pigments, adhesives, joint cements, metalworking fluids, paper, inks, waxes, household products, and cosmetics. As a biocide protects water-based systems from bacteria, fungi, yeast and algae.
5-(Hydroxymethyl)-2-furfural	[67-47-0]	TR-554	A decomposition product of carbohydrates and is formed during cooking or heat sterilization of food. It has been identified in a wide variety of heat processed foods including milk, fruit juices, spirits, honey, etc. It is also found in cigarette smoke.
Isoeugenol	[97-54-1]	TR-551	Food flavoring agent; fragrance; in manufacture of vanillin. Found in cloves, tobacco, other plants, and flowers.

Table 22: Technical Reports Published During FY 2008

Chemical/Exposure–Study Type	[CASRN]	Technical Report Number	Use
Propargyl alcohol Inhalation – Toxicology and Carcingenesis	[107-19-7]	TR-552	Reactant/chemical intermediate, pharmaceutical intermediate, soil fumigant, corrosion inhibitor, solvent stabilizer, and polymer modifier.
Cresols Feed – Toxicology and Carcingenesis	[1319-77-3]	TR-550	High volume chemicals with a variety of industrial uses.
Sodium Dichromate Dihydrate Drinking Water – Toxicology and Carcingenesis	[7789-12-0]	TR-546	Contaminant resulting from various industrial processes.
Genistein Feed – Toxicology and Carcingenesis	[446-72-0]	TR-545	Naturally occurring isoflavone in soy products.
α-Methylstyrene Inhalation – Toxicology and Carcingenesis	[98-83-9]	TR-543	Used in the production of acrylonitrile-butadiene-styrene resins and copolymers; used as plasticizers in paints, waxes, adhesives, and plastics.
Formamide Gavage – Toxicology and Carcinogenesis	[75-12-7]	TR-541	Used as a softener for paper, gums, and animal glues; as an ionizing solvent; and in the manufacture of formic esters and hydrocyanic acid.
Methylene blue trihydrate Gavage – Toxicology and Carcingenesis	[7720-79-3]	TR-540	A variety of biomedical and biologically therapeutic applications.
Genistein Feed - Multigenerational Reproductive Toxicology	[446-72-0]	TR-539	Naturally occurring isoflavone in soy products.

Levels of Evidence of Carcinogenic Activity			
Male Rats	Female Rats	Male Mice	Female Mice
N/A	N/A	In general, in SKH-1 mice treated topically with aloe, the onset, incidence, and multiplicity of in-life observed skin lesions and the incidence of squamous cell neoplasms (papilloma, carcinoma *in situ*, and carcinoma) did not differ from controls; See report for complete results.	
Clear Evidence	Clear Evidence	Clear Evidence	Clear Evidence
Equivocal Evidence	No Evidence	No Evidence	No Evidence
Clear Evidence	Some Evidence	Clear Evidence	Clear Evidence
No Evidence	No Evidence	No Evidence	No Evidence
No Evidence	No Evidence	No Evidence	Some Evidence
Equivocal Evidence	No Evidence	Clear Evidence	Equivocal Evidence

Levels of Evidence of Carcinogenic Activity			
Male Rats	Female Rats	Male Mice	Female Mice
Some Evidence	No Evidence	Some Evidence	Some Evidence
Equivocal Evidence	Not tested	Not tested	Some Evidence
Clear Evidence	Clear Evidence	Clear Evidence	Clear Evidence
WITH CONTINUOUS EXPOSURE			
No Evidence	Some Evidence	Not tested	Not tested
EXPOSURE THROUGH 20 WEEKS			
No Evidence	Equivocal Evidence	Not tested	Not tested
WITH EXPOSURE OF OFFSPRING OF 3 PRIOR GENERATIONS OF EXPOSURE			
No Evidence	Equivocal Evidence	Not tested	Not tested
Some Evidence	No Evidence	Equivocal Evidence	Clear Evidence
No Evidence	No Evidence	Clear Evidence	Equivocal Evidence
Some Evidence	No Evidence	Some Evidence	Equivocal Evidence

See report for results

Table 23: Genetically Modified Models Reports Published During FY 2008

Chemical/ Exposure-Study Type	[CASRN]	Technical Report Number	Use	Levels of Evidence of Carcinogenic Activity	
Glycidol Gavage – Toxicology and Carcingenesis	[556-52-5]	GMM-13	Used as a chemical intermediate in the pharmaceutical industry, and in the synthesis of glycerol, glycidyl ethers, and amines; as a stabilizer in the manufacture of vinyl polymers.	Haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mice	
				Male	Female
				Clear evidence	Some evidence
Phenolphthalein Feed – Toxicology and Carcingenesis	[77-09-8]	GMM-12	Commonly used as a laxative; decreasing usage in US	Haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mice	
				Male	Female
				No evidence	No evidence
Benzene Gavage – Toxicology and Carcingenesis	[71-43-2]	GMM-08	Used primarily as a solvent in the chemical and pharmaceutical industries, and as a starting material and intermediate in the synthesis of numerous chemicals, and in gasoline.	Haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mice	
				Male	Female
				Clear evidence	No evidence
Allyl Bromide Dermal and Gavage – Toxicology and Carcingenesis	[106-95-6]	GMM-07	Used as a starting material/chemical intermediate in organic synthesis and in the manufacture of polymers/resins, synthetic perfumes, pharmaceuticals, agricultural chemicals, and other allyl compounds.	Haploinsufficient B6.129-Trp53 ^{tm1Brd} (N5)] mice	
				Male	Female
				No evidence	No evidence

Note: Only summaries of carginogenicity conclusions are included in the tables.
Complete information is available in the full study reports found at *http://ntp.niehs.nih.gov/.*

NTP anticipates six Technical Reports will undergo peer review in FY 2009 as shown in Table 24.

Table 24: Technical Reports Planned for Peer Review in 2009

Chemical	[CASRN]	Technical Report Number	Use
Androstenedione	[63-05-8]	TR-560	A natural androgen steroid hormone synthesized within men and women. It is an intermediate in the synthesis of testosterone and other pharmaceutical steroids, including oral contraceptives and topical anti-inflammatory products. Also used as a dietary supplement by athletes (prior to banning of over the counter sales).
Goldenseal root powder		TR-562	Goldenseal root powder is used in folk medicine for the treatment of gastrointestinal disturbances, urinary disorders, hemorrhage, skin, mouth, and eye infections, and inflammation.
beta-Myrcene	[123-35-3]	TR-557	Intermediate in the commercial production of terpene alcohols which serve as intermediates for the production of large-volume aroma and flavor chemicals. Used as scenting agents in cosmetics, soaps, and detergents. Beta-myrcene is a peripheral analgesic substance and the active ingredient in lemongrass tea. Identified in over 200 plants and detected in emissions of plywood veneer dryers.
Polychlorinated biphenyl 118 (toxic equivalency factor evaluation)	[31508-00-6]	TR-559	One of the banned polychlorinated biphenyls, formerly used as an industrial insulator and lubricant.
3,3',4,4'-Tetrachloroazobenzene	[14047-09-7]	TR-558	An impurity formed as an unwanted by-product in the manufacture of 3,4-dichloroaniline and its herbicidal derivatives Propanil,® Linuron,® and Diuron®; occurs from the degradation of chloroanilide herbicides (acylanilides, phenylcarbamates, and phenylureas) in soil by peroxide-producing microorganisms; and is formed by the photolysis and biolysis of 3,4-dichloroaniline.
Tetralin	[119-64-2]	TR-561	Used as an industrial solvent primarily for naphthalene, fats, resins, oils, and waxes; as a solvent and stabilizer for shoe polishes and floor waxes; as a solvent for pesticides, rubber, asphalt, and aromatic hydrocarbons; as a dye solvent carrier in the textile industry; as a substitute for turpentine in lacquers, paints, and varnishes; in paint thinners and as a paint remover; in alkali-resistant lacquers for cleaning printing ink from rollers and type; as a constituent of motor fuels and lubricants; for the removal of naphthalene in gas distribution systems; and as an insecticide for clothes moths.

General Toxicology Studies

The NTP performs prechronic toxicity studies to provide dose-setting information for chronic studies and to address specific deficiencies in the toxicology database for the chemical such as an understanding of toxicity with repeated exposures.

Although designs are flexible, prechronic studies usually involve exposures of rats and mice of both sexes to substances for periods of 14 to 90 days. Assessments almost always include tissue histopathology, clinical pathology, and sperm motility or measurements of estrous cycle length. A determination of the frequency of micronucleated erythrocytes is conducted as an *in vivo* measure of genotoxic potential. The study protocol may include more detailed or focused studies when findings published in the existing scientific literature or identified in initial NTP studies suggest a target organ or system. The study protocol may include separate studies of reproductive, genetic, or immunological toxicity based on the outcome of the toxicity screens and may use additional endpoints to improve our understanding of the mechanisms and modes of action of a chemical.

In some cases, the NTP uses alternative models, including genetically modified mouse models and non-mammalian models, for prechronic studies. Such studies are presented in the section "Alternative Test Systems" (page 80). The following tables list the toxicity studies that were ongoing, initiated, completed and published during FY 2008. Information is available at *http://ntp.niehs.nih.gov/go/reports*. Table 29 lists toxicity studies that are planned for FY 2009.

Table 25: Ongoing Prechronic Toxicity Studies During FY 2008

Chemical	[CASRN]	Species/Strain	Study Route	Length	Project Leader
Black cohosh	[84776-26-1]	Rats: Wistar Han	Gavage	90 days	Stout
2,3-Butanedione	[431-03-8]	Mice: B6C3F1 Rats: Wistar Han	Inhalation	90 days	Morgan
Ethanone, 1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-(Iso-E Super)	[54464-57-2]	Mice: B6C3F1 Rats: F344/NTAC	Topical application	90 days	Chan
Metal working fluids (Trim VX)		Mice: B6C3F1 Rats: Wistar Han	Inhalation	90 days	Kirby
Nanoscale material (Fullerene-C60 1 micron)	[99685-96-8]	Mice: B6C3F1 Rats: Wistar Han	Inhalation	90 days	Walker
Nanoscale material (Fullerene-C60 50 nanometers)	[99685-96-8]	Mice: B6C3F1 Rats: Wistar Han	Inhalation	90 days	Walker
Resveratrol	[501-36-0]	Mice: B6C3F1 Rats: F344/NTAC Rats: Wistar Han	Gavage	14 days 90 days	Germolec
Serotype 5 Adeno-associated Viral Vector (rAAV5SCTLA4:Ig)		Mice: BALB/c	Intraductal cannulation	90 days	Irwin
3,3',4,4'-Tetrachloroazobenzene	[14047-09-7]	Rats: Sprague-Dawley	Gavage	18 days 5 weeks	Hooth
p-Toluenesulfonamide	[70-55-3]	Mice: B6C3F1 Rats: F344/NTAC	Dosed-feed	14 days 90 days	Dunnick

Table 26: Toxicity Studies Initiated during FY 2008

Chemical	[CASRN]	Species/Strain	Study Route	Length	Project Leader
Antimony trioxide	[1309-64-4]	Mice: B6C3F1 Rats: Wistar Han	Inhalation	14 days	Stout
Black cohosh	[84776-26-1]	Rats: Wistar Han	Gavage	90 days	Stout
2,3-Butanedione	[431-03-8]	Mice: B6C3F1 Rats: Wistar Han	Inhalation	90 days	Morgan
Di(2-ethylhexyl) phthalate	[117-81-7]	Monkey: Rhesus	IV Injection/ oral	14 days	Delclos
Lipopolysaccharide (Airways Disease Project)		Mice: 129S1/SvImJ Mice: C57BL/6J (Jackson)	Inhalation	1 day 1 day	Bucher
Metal working fluids (Trim VX)		Mice: B6C3F1 Rats: Wistar Han	Inhalation	90 days	Kirby
Nanoscale material (Fullerene-C60 1 micron)	[99685-96-8]	Mice: B6C3F1 Rats: Wistar Han	Inhalation	90 days	Walker
Nanoscale material (Fullerene-C60 50 nanometers)	[99685-96-8]	Mice: B6C3F1 Rats: Wistar Han	Inhalation	90 days	Walker
Ozone (Airways Disease Project)	[10028-15-6]	Mice: DBA/2J	Inhalation	1 day	Bucher
Serotype 5 Adeno-associated Viral Vector (rAAV5SCTLA4:Ig)		Mice: BALB/c	Intraductal cannulation	90 days	Irwin
Serotype 2 Adeno-associated Viral Vector rAAVhEpo		Mice: BALB/c	Intraductal cannulation	90 days	Irwin

Table 27: Toxicity Studies Completed during FY 2008

Chemical	[CASRN]	Species/Strain	Study Route	Length	Project Leader
Allergen (Airways Disease Project)		Mice: A/J Mice: C57BL/6J (Jackson)	IP Injection/	1 day	Bucher
Antimony trioxide	[1309-64-4]	Mice: B6C3F1 Rats: Wistar Han	Inhalation	14 days	Stout
Chitosan	[9012-76-4]	Rats: Sprague-Dawley	Dosed-Feed	26 weeks	Chhabra
Cigarette smoke (Airways Disease Project)		Mice: C57BL/6J (Jackson)	Inhalation	1 day	Bucher
Di(2-ethylhexyl) phthalate	[117-81-7]	Monkey: Rhesus	IV Injection/ Oral	14 days	Stout
Insertional mutagenesis (LTR/SIN vectors)		Mice: B6.SJL-Ptprc[a] Pepc[b]/BoyJ	Intravenous	12 weeks	Irwin
Lipopolysaccharide (Airways Disease Project)		Mice: 129S1/SvImJ Mice: C57BL/6J (Jackson)	Inhalation	1 day 1 day	Bucher
Ozone (Airways Disease Project)	[10028-15-6]	Mice: DBA/2J	Inhalation	1 day	Bucher
QT drugs (bepridil hydrochloride)	[74764-40-2]	Dog: Beagles	Per Os (Capsule)	14 days 90 days	Hooth
QT drugs (Loratadine)	[79794-75-5]	Dog: Beagles	Per Os (Capsule)	14 days 90 days	Hooth
Senna (powdered)*	8013-11-4	Mice: P53 +/- (C57BL/6)	Dosed-Feed	39 weeks	Dunnick

**indicates study performed using genetically modified model*

Table 28: NTP Toxicity Reports Published During FY 2008				
Chemical/Study Type	**[CASRN]**	**Technical Report Number**	**Use**	**Findings**
Genistein Reproductive Dose Range-Finding	[446-72-0]	TOX-79	Naturally occurring isoflavone in soy products.	Evidence of the potential of dietary genistein to affect multiple estrogen-sensitive organs in both male and female rats. Data were used in selecting doses for the subsequent multigenerational and chronic toxicity studies at 5 to 500 ppm.
Wy-14,643 Toxicity	[50892-23-4]	TOX-62	To lower serum cholesterol; it is not used in clinical applications.	Exposure to Wyeth-14,643 caused several changes in the livers of male rats, mice, and hamsters, including increased liver weights, increases in cytoplasmic alteration of the liver, and some liver foci. Wyeth-14,643 also had effects on the testes of exposed male rodents, decreasing the spermatid counts and the weights of the cauda epididymis.

Note: Only summaries of finding are included in the tables. Complete information is available in the full study reports found at *http://ntp.niehs.nih.gov/.*

Table 29: Toxicity Studies Planned for FY 2009*					
Chemical	**[CASRN]**	**Species/Strain**	**Study Route**	**Length**	**Project Leader**
Acetoin	[513-86-0]	Mice: B6C3F1 Rats: Wistar Han	Inhalation	14 days 90 days	Morgan
Cell phone radiation (code division multiple access)		Mice: B6C3F1 Rats: Sprague-Dawley	Whole body exposure	49 days 5 days	Wyde
Cell phone radiation (global system for mobile communications)		Mice: B6C3F1 Rats: Wistar Han	Whole body exposure	49 days 5 days	Wyde
Metal working fluids (Syntilo 1023)		Mice: B6C3F1 Rats: Wistar Han	Inhalation	90 days	Kirby
ortho-Phthalaldehyde	[643-79-8]	Mice: B6C3F1 Rats: Harlan Sprague-Dawley	Inhalation	90 days	Wyde
Usnea barbata, extract and usnic acid	[84696-53-7]	Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-),Rats: F344 (NCTR)	Dosed-feed	14 days 90 days	Leakey

**Known test articles as of 10/01/2008. Others may be scheduled as protocols are finalized.*

Mutagenesis and Genetic Toxicity

Genetic toxicity test results are used to make decisions about whether a substance should be tested for carcinogenicity in rodents; to aid in the interpretation of toxicity, carcinogenicity, or other *in vivo* test results; and to provide a database for use in structure-activity analyses. Testing is conducted at contract laboratories.

Analysis of the early, multi-test database showed that positive results for a chemical in the Salmonella gene mutation assay were highly correlated with carcinogenicity in multiple species/sexes of rodents and at multiple tissue sites; data from additional tests did not improve the correlation. Subsequently, studies of the correlation between mutagenicity test data and rodent carcinogenicity showed a strong association between clearly positive results in long-term mouse peripheral blood micronucleus tests and rodent carcinogenicity. The importance of genetic toxicity test data in assessing exposure hazard for NTP chemicals is underscored by the fact that most organic chemicals (other than hormones) identified by the International Agency for Research on Cancer (IARC) as human carcinogens are genotoxic, and the vast majority of them are detected by both the Salmonella assay and rodent micronucleus tests. Additional assays may be conducted with certain chemicals to gain further insight into the types of DNA and chromosomal damage induced by a chemical.

Gene mutations and DNA damage are examined in most tissues; cytogenetic effects, measured as the induction of micronuclei, are generally examined in bone marrow cells or in peripheral erythrocytes. The erythrocyte studies are integrated with other toxicity evaluations to minimize the use of animals and expand the toxicology information for the chemical in the same animals. Substances tested for genetic toxicity during FY 2008 are listed in Table 30. Information is available at *http://ntp.niehs.nih.gov/go/reports*.

Table 30: Ongoing and Completed Genetic Toxicity Studies During FY 2008

Chemical	[CASRN]	Testing Battery
Acetylacetone	[123-54-6]	Micronucleus
Acrylamide	[79-06-1]	Micronucleus
Aloe vera charcoal filtered whole leaf extract		Salmonella
Aloe vera gel	[8001-97-6]	Salmonella
Aloe vera whole leaf extract (native)		Salmonella
2-Aminoanthracene	[613-13-8]	Salmonella
Ammonium metavanadate	[7803-55-6]	Salmonella
Benzyl chloride	[100-44-7]	Salmonella
Bixin	[6983-79-5]	Micronucleus
Black cohosh	[84776-26-1]	Micronucleus
Bromochloroacetic acid	[5589-96-8]	Salmonella
tert-Butylacrylamide	[107-58-4]	Micronucleus
Dibromoacetonitrile	[3252-43-5]	Salmonella
1,3-Dichloro-2-propanol	[96-23-1]	Micronucleus
N,N-Dimethylacetoacetamide	[2044-64-6]	Micronucleus
Dimorpholinodiethyl ether	[6425-39-4]	Salmonella

Chemical	[CASRN]	Testing Battery
Emtricitabine	[143491-57-0]	Micronucleus
Epichlorhydrin	[106-89-8]	Micronucleus
N-Ethyl acetoacetamide	[10138-46-2]	Salmonella
N-Ethyl acetoacetamide	[10138-46-2]	Micronucleus
2-Ethylhexyl-*p*-methoxycinnamage	[5466-77-3]	Salmonella
Ethyl methanesulfonate	[62-50-0]	Micronucleus
Fennel seed oil sweet	[8006-84-6]	Salmonella
Hesperidin	[520-26-3]	Salmonella
Hydroxyurea	[127-07-1]	Micronucleus
Imidazolidinyl urea	[39236-46-9]	Micronucleus
Ionic liquid (1-butyl-1-methylpyrrolidinium chloride)	[479500-35-1]	Salmonella
Ionic liquid (1-butyl-3-methylimidazolium chloride)	[79917-90-1]	Salmonella
Ionic liquid (1-ethyl-3-methylimidazolium acetate)	[143314-17-4]	Salmonella
Ionic liquid (1-ethyl-3-methylimidazolium chloride)	[65039-09-0]	Salmonella
Ionic liquid (*n*-butylpyridinium chloride)	[1124-64-7]	Salmonella
Labdanum, oil	[8016-26-0]	Salmonella
Lavender oil	[8000-28-0]	Salmonella
alpha-Lipoic acid	[62-46-4]	Salmonella
Metal working fluids (CIMSTAR 3800)		Salmonella
Metal working fluids (CIMSTAR 3800)		Micronucleus
Metal working fluids (Trim SC210)		Micronucleus
2-Methoxy-4-nitroaniline	[97-52-9]	Salmonella
N-Methyl-3-oxobutyramide	[20306-75-6]	Micronucleus
Methylphenidate hydrochloride	[298-59-9]	Micronucleus
Nanoscale material (Fullerene-C60 1 micron)	[99685-96-8]	Micronucleus
Nanoscale material (Fullerene-C60 50 nanometers)	[99685-96-8]	Micronucleus
1-Naphthalenesulfonic acid, 6-diazo-5,6-dihydro-5-oxo, sodium salt	[2657-00-3]	Salmonella
d-Neomenthol	[2216-52-6]	Salmonella
2-Nitroethanol	[625-48-9]	Micronucleus
2-Nitroethanol	[625-48-9]	Salmonella
Norbixin (cis/trans mixture)	[542-40-5]	Micronucleus
Nutlin 3	[548472-68-0]	Salmonella
3-Oxobutanamide	[5977-14-0]	Micronucleus
Pelargonic acid	[112-05-0]	Salmonella
ortho-Phthalaldehyde	[643-79-8]	Salmonella
Pubertal vinclozolin study	[50471-44-8]	Micronucleus
Senna (powdered)	[8013-11-4]	Micronucleus

Chemical	[CASRN]	Testing Battery
Sodium azide	[26628-22-8]	Salmonella
Sodium orthovanadate	[13721-39-6]	Salmonella
Sodium vanadate (V)	[13718-26-8]	Salmonella
Tenofovir	[147127-20-6]	Micronucleus
Tetrabromo-o-cresol	[576-55-6]	Micronucleus
Tetralin	[119-64-2]	Salmonella
Transgenic model evaluation (Cyclophosphamide monohydrate)	[6055-19-2]	Micronucleus
4,7,10-Trioxatridecane-1.13-diamine	[4246-51-9]	Salmonella
Vanadyl sulfate	[28884-13-6]	Salmonella
Vincristine sulfate salt	[2068-78-2]	Micronucleus
Water	[7732-18-5]	Salmonella

Organ System Toxicity

Nervous System, Developmental, and Reproductive Toxicity

Behavioral and neurologic alterations in response to deleterious environmental agents often represent the earliest observable manifestation of toxicity. The testing batteries examine the various neurobehavioral systems: sensory, motor, autonomic, and peripheral nervous system. The FOB employs observational screening while the NIEHS test battery uses automated test systems to evaluate the various nervous system components.

As part of its charge to test chemicals of concern for potential toxicity the NTP evaluates developmental and reproductive toxicity primarily by using teratology and Reproductive Assessment by Continuous Breeding (RACB) study designs (*http://ntp.niehs.nih.gov/go/33668*). The RACB study design was developed by the NTP for use to identify potential hazards to toxic effects on male and/or female reproduction, characterize that toxicity, and define the dose-response relationships for each compound. The study design has evolved over the years; initially the study employed predominantly mice as the test species and now almost exclusively uses rats. As our improved knowledge and use of sensitive end points has increased, they have been incorporated into revisions of the study design. Table 31 lists completed and ongoing neurotoxicity, developmental, and reproductive studies during FY 2008 and Table 32 lists studies planned for FY 2009.

Table 31: Ongoing and Completed Organ Systems Toxicity Studies During FY 2008

Chemical	[CASRN]	Species/Strain	Route	Project Leader	Testing Battery
Bitter orange or *p*-Synephrine	[94-07-5]	Rats: Sprague-Dawley	Gavage	Hansen	Teratology
Bitter orange with caffeine		Rats: Sprague-Dawley	Gavage	Hansen	Teratology
Acrylamide	[79-06-1]	Rats: F344: (NCTR)	Gavage	Beland	Neurotoxicity Assessment
Ketamine hydrochloride	[1867-66-9]	Rats: Sprague-Dawley (NCTR)	Subcutaneous Injection		Neurotoxicity Assessment

Table 32: RACB Studies Planned for FY 2009				
Chemical	**[CASRN]**	**Species/Strain**	**Route**	**Testing Battery**
AZT/3TC/Nelfinavir mesylate combination		Mice: Swiss CD-1	Gavage	RACB
AZT/3TC/Nelfinavir combination		Mice: Swiss CD-1	Gavage	RACB
n-Butyl glycidyl ether	[2426-08-6]	Rats: Wistar Han	TBD	RACB

Immunotoxicity

NTP immunotoxicity studies address adverse effects on the immune system that may result from exposure to environmental chemicals, biological materials, or therapeutic agents. The identification of substances that have potential to cause injury to the immune system is of considerable public health significance as alterations in immune function can lead to increased incidence of hypersensitivity disorders, autoimmune or infectious disease, or neoplasia. Immunotoxicity can be divided into two broad research areas: (1) studies of altered hematopoietic (blood cell development) or immunologic events associated with exposure of humans and animals to chemicals and (2) studies of immune-mediated hypersensitivity (allergy and autoimmunity) resulting from exposure to environmental chemicals or therapeutics. In the former case, the immune system acts as a passive target (nonspecific) for the xenobiotic, and the result may be an increased incidence or severity of infectious disease or neoplasia because of the inability to respond adequately to the invading agent. In hypersensitivity (i.e., allergy), the immune system responds to small molecular weight compounds that bind to host tissue, recognizing the complex as foreign antigen. This immune response to the chemical-host tissue complex may lead to a disease, such as respiratory tract allergies (e.g., asthma, rhinitis) or allergic contact (skin) dermatitis. Autoimmunity, another form of immune-mediated disease, is characterized by an immune response against constituents of the body's own tissues (autoantigens). Table 33 lists completed and ongoing immuntoxicity studies during FY 2008.

Table 33: Ongoing and Completed Immunotoxicity Studies During FY 2008					
Chemical	**[CASRN]**	**Species/Strain**	**Route**	**Project Leader**	**Testing Battery**
Annatto	[1393-63-1]	Mice: BALB/c	Topical application	Germolec	Hypersensitivity
Bixin [6983-79-5]		Mice: BALB/c	Topical application	Germolec	Hypersensitivity
Nanoscale material (Fullerene-C60 1 micron)	[99685-96-8]	Rats: Wistar Han	Inhalation	Walker	Immunomodulation
Autumn Sunset True Color Concentrate		Mice: CBA/ Ca Jackson	Subcutaneous injection	Howard (NCTR)	Hypersensitivity
3'-Azido-3'-deoxythymidine (AZT)	[30516-87-1]	Mice: B6C3F1	Gavage	Germolec	Immunomodulation Developmental
2,3-Butanedione	[431-03-8]	Mice: BALB/c application	Topical	Germolec	Hypersensitivity
2,3-Butanedione	[431-03-8]	Mice: BALB/c	Inhalation	Germolec	Hypersensitivity
tert-Butyl hydroperoxide	[75-91-2]	Mice: BALB/c application	Topical	Germolec	Hypersensitivity

Chemical	[CASRN]	Species/Strain	Route	Project Leader	Testing Battery
o-Cresol	[95-48-7]	Mice: BALB/c Application	Topical	Germolec	Hypersensitivity
Dibenz(a,h)anthracene	[53-70-3]	Mice: B6C3F1	Gavage	Germolec	Immunomodulation
Dibenz(a,h)anthracene	[53-70-3]	Mice: B6C3F1	Gavage	Germolec	Developmental Immunomodulation
Dimethylamine borane	[74-94-2]	Mice: BALB/c	Topical application	Germolec	Hypersensitivity
Disulfoton[298-04-4]		Mice: B6C3F1	Gavage (Range-finding)	Germolec	Immunomodulation
Double Dark Fudge True Color Concentrate		Mice: CBA/ Ca (Jackson)	Subcutaneous injection	Howard	Hypersensitivity
Double Fudge Concentrate		Mice: CBA/ Ca (Jackson)	Subcutaneous injection	Howard (NCTR)	Hypersensitivity
Echinacea purpurea, ext.	[90028-20-9]	Mice: B6C3F1	Gavage	Germolec	Immunomodulation
Elmiron (sodium pentosanpolysulfate)	[37319-17-8]	Mice: B6C3F1	Gavage	Germolec	Immunomodulation
Ethanone, 1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-Tetramethyl-2-Naphthalenyl)-(Iso-E Super)	[54464-57-2]	Mice: BALB/c	Topical application	Germolec	Hypersensitivity
Genistein	[446-72-0]	Mice: Non-obese Diabetic	Gavage	Germolec	Autoimmunity
Gum guggul extract		Mice: B6C3F1	Gavage	Germolec	Immunomodulation
Heptachlor	[76-44-8]	Mice: BALB/c	Topical application	Germolec	Hypersensitivity
Lovastatin	[75330-75-5]	Mice: B6C3F1	Gavage (Range-finding)	Germolec	Immunomodulation
Monoclonal antibody protein therapeutics (CD-4)		Mice: B6C3F1	Intraperitoneal injection	Germolec	Immunomodulation
Monoclonal antibody protein therapeutics (CD-8)		Mice: B6C3F1	Intraperitoneal injection	Germolec	Immunomodulation
Nanoscale material (Fullerene-C60 1 micron)	[99685-96-8]	Mice: B6C3F1	Inhalation	Walker	Immunomodulation
Nanoscale material (Fullerene-C60 50 nanometers)	[99685-96-8]	Rats: Wistar Han	Inhalation	Walker	Immunomodulation
Nanoscale material (Fullerene-C60 50 nanometers)	[99685-96-8]	Mice: B6C3F1	Inhalation	Walker	Immunomodulation
1,5-Naphthalene diisocyanate	[3173-72-6]	Mice: BALB/c	Topical application	Germolec	Hypersensitivity
Nelfinavir mesylate	[159989-65-8]	Mice: B6C3F1	Gavage	Germolec	Immunomodulation
Nelfinavir mesylate	[159989-65-8]	Mice: B6C3F1	Gavage	Germolec	Developmental
Nevirapine	[129618-40-2]	Mice: B6C3F1	Gavage	Germolec	Immunomodulation Developmental

Chemical	[CASRN]	Species/Strain	Route	Project Leader	Testing Battery
Norbixin (cis/trans mixture)	[542-40-5]	Mice: BALB/c	Topical	Germolec application	Hypersensitivity
Phenol [108-95-2]		Mice: B6C3F1	Dosed-water	Germolec	Immunomodulation
Resveratrol	[501-36-0]	Mice: B6C3F1	Gavage	Germolec (Range-finding)	Immunomodulation
Rosewood True Color Concentrate		Mice: CBA/ Ca Jackson	Subcutaneous injection	Howard (NCTR)	Hypersensitivity
3,3',4,4'-Tetrachloroazobenzene	[14047-09-7]	Rats: Sprague-Dawley	Gavage	Germolec	Immunomodulation

Disposition, Metabolism and Toxicokinetic Studies

Complete dosimetry of a chemical or physical agent describes its absorption, distribution, metabolism, and elimination (ADME) at differing levels of exposure, over all ages, via multiple routes of exposure, and under varying genetic backgrounds in humans and test animals. Data from NTP chemical disposition, metabolism, and toxicokinetic studies are used in these efforts. Those substances evaluated during FY 2008 are listed in Table 34 and studies planned for FY 2009 are listed in Table 35. Most studies are conducted in intact laboratory animals; some require incubations of human and rodent liver slices with the chemical. This information provides dosimetric data that can be integrated with other anatomical, biochemical, and physiological information into development of biochemical and physiologically based pharmacokinetic models. Such models are used increasingly in risk assessment to extrapolate between species, across dose ranges, and across different routes of exposure.

Table 34: Ongoing and Completed Disposition, Metabolism and Toxicokinetic Studies During FY 2008

Chemical	[CASRN]	Species/Strain	Route	Project Leader
5-Amino-o-cresol	[2835-95-2]	Mice: B6C3F1 Rats: F344/N	Gavage Topical application	
Anethole	[104-46-1]		*in-vitro*	Waidyanatha
Benzene	[71-43-2]	Mice: 129S1/SvImJ Mice: A/J Mice: AKR/J Mice: B6C3F1 Mice: BTBR T+ tf/J 2 Mice: Balb/cByJ Mice: C3H/HeJ Mice: C57BL/6 Mice: CAST/EiJ (M. m. castaneus) Mice: DBA/2 Jackson Mice: FVB/NJ Mice: KK/HIJ Mice: MOLF/EiJ (M. m. molossinus) Mice: NOD/LtJ Mice: NZW/LacJ Mice: PWD/PhJ (M. m. musculus) Mice: WSB/EiJ (M. m. domesticus)	Gavage	Cunningham
2,2-bis(Bromomethyl)-1, 3-propanediol	[3296-90-0]		*in-vitro*	Cunningham
2,3-Butanedione	[431-03-8]		*in-vitro*	Waidyanatha
Cumene	[98-82-8]	Mice: B6C3F1 Rats: F344/N	Gavage	Sanders

Chemical	[CASRN]	Species/Strain	Route	Project Leader
N,N-Dimethylacetoacetamide	[2044-64-6]	Rats: F344/N Charles River	Gavage	Waidyanatha
Estragole	[140-67-0]		*in-vitro*	Waidyanatha
Eugenol	[97-53-0]		*in-vitro*	Waidyanatha
Ionic liquid (1-butyl-3-methylimidazolium chloride)	[79917-90-1]	Mice: B6C3F1 Rats: F344/N	Gavage Intravenous Topical application	Cunningham
Ionic liquid (1-butyl-1-methylpyrrolidinium chloride)	[479500-35-1]	Mice: B6C3F1 Rats: F344/N	Gavage Intravenous Topical application	Cunningham
Ionic liquid (*n*-butylpyridinium chloride)	[1124-64-7]	Mice: B6C3F1 Rats: F344/N	Gavage Intravenous Topical application	Cunningham
Isoeugenol	[97-54-1]		*in-vitro*	Waidyanatha
Isosafrole	[120-58-1]		*in-vitro*	Waidyanatha
Methyleugenol	[93-15-2]		*in-vitro*	Waidyanatha
Myristicin	[607-91-0]		*in-vitro*	Waidyanatha
Nanoscale material (Fullerene C60)	[99685-96-8]	Rats: F344/N	Insufflation Intratracheal Intravenous	Sanders
Nanoscale material (Quantum dots)		Mice: SKH-1 Hairless	Subcutaneous injection Topical application	Howard
Nanoscale TiO_2				NCTR

Table 35: Disposition, Metabolism and Toxicokinetic Studies Planned for FY 2009*

Chemical	[CASRN]	Species/Strain	Route
2,3-Butanedione	[431-03-8]	Mice: B6C3F1 Rats: Sprague-Dawley	Intratracheal Oropharyngeal
n-Butyl-*p*-hydroxybenzoate	[94-26-8]	Rats: Sprague-Dawley	Gavage Intravenous Topical application
1,3-Dichloro-2-propanol	[96-23-1]	Mice: B6C3F1 Rats: Sprague-Dawley	Gavage
Dimethylamine borane	[74-94-2]	Human (*in vitro*) Rats: Sprague-Dawley	Gavage Intravenous, Topical application *in-vitro*
2',2'''-Dithiobisbenzanilide	[135-57-9]	Human (*in vitro*) Mice: TBD Rats: TBD	*in-vitro*
2-Hydroxy-4-methoxybenzophenone	[131-57-7]	Mice: TBD Rats: TBD	Multiple routes
2-Methoxy-4-nitroaniline	[97-52-9]	Mice: B6C3F1 Rats: Sprague-Dawley	Gavage Intravenous Topical application

**Known test articles as of 10/01/2008. Others may be scheduled as protocols are finalized*

Cellular and Molecular Pathology

NTP Biomarker Project

NTP organized a workshop ‘‘Biomarkers for Toxicology Studies’’ to help identify end points that could be added routinely to toxicity studies to provide more confidence that NTP studies adequately screen for changes in heart and lung disease/function and lipid and carbohydrate metabolism. The outcome of the workshop was published in 2007 (Toxicol. Sci., 100(1), 29-35). The biomarkers serum cholesterol and triglycerides were added to the routine testing regimen. This information was presented at the 47th Annual SOT Meeting, March 2008. For information contact Dr. Gregory Travlos, *travlos@niehs.nih.gov*.

Bone Marrow Evaluations

A joint effort between the American Society of Veterinary Clinical Pathology and the Society of Toxicologic Pathologists (STP) organized a “Bone Marrow Evaluation Working Group.” The goal was to prepare a document that reviewed regulations and relevant literature and provided best practice recommendations addressing the examination of bone marrow in nonclinical toxicity and carcinogenicity studies. A draft of the document has been prepared and is scheduled to be presented at the next annual meeting of the STP (June 2009). For information contact Dr. Gregory Travlos, *travlos@niehs.nih.gov*.

Immuntoxicology Pathology Peer Review

Because of a constant effort to improve data quality, the NTP decided to apply the same level of rigorous pathology peer review to its immunotoxicology studies as it has traditionally applied to its subchronic and chronic carcinogenicity bioassays. This effort has included both the development of NTP specifications and pathology training for these studies. An NTP Immunotoxicity Study Pathology Specifications document was developed in 2008 that provides guidelines and addresses the specifics of study details and pathology review processes. To address pathology training for enhanced histopathology of lymphoid organs, the NTP Workshop on Pathology for Immunotoxicity Studies was held December 2007. For information contact Dr. Susan Elmore, *elmore@niehs.nih.gov*.

Reproductive and Developmental Toxicology Pathology Peer Review

As with the immunotoxicology studies, the NTP has decided to apply the same rigorous pathology peer review process to its reproductive and developmental toxicity studies. These RACB studies, have been redesigned to provide a more complete picture of the potential for agents to cause reproductive and developmental toxicity. An NTP Reproductive and Developmental Toxicity Study Pathology Specifications document is being developed (to be completed by June 2009) that will provide guidelines and address the specifics of study details and pathology review processes. To address pathology training for gross and histopathologic evaluation of tissues for these studies, the NTP Workshop on Pathology of the Reproductive Tract was held in October 2008. Additionally, a histopathologic atlas of the reproductive tract of male and female rats is being developed to assist pathologists reading these studies. For information contact Dr. Mark Cesta, *cesta@niehs.nih.gov*.

Atlas for Documenting Normal Anatomical Structures in Embryos

There has been a need in the toxicologic pathology community for illustrative material to aid in the phenotyping of transgenic embryos. Since the rapid progression of transgenic technologies, the mouse has become the major animal model of defective development. A single reference reviewing and describing the anatomy and histology of normal developmental events, stage by stage, in color and high magnification has not been available. To address this need, NTP scientists are producing atlases of various mouse embryo organ systems. The aim of these color atlases, demonstrating embryonic/fetal organ development, is to provide a tool for pathologists and biomedical scientists to use for detailed,

histological evaluation of hematoxylin and eosin-stained sections of the developing mouse. These atlases will provide a histological account of the normal development of each organ system with sagittal, transverse and coronal sections having detailed labeled landmarks and description of normal histology. Although the focus is on normal anatomy and histology, these atlases will also present illustrations and discussion of the most common spontaneous and induced lesions.

The embryo heart atlas has been completed and the hepatobiliary and central nervous system atlases are currently in preparation. Future atlases will include organ systems such as genitourinary, skeletal, respiratory, and gastrointestinal. Each publication includes detailed text of significant embryonic development at each day, high magnification histology sections, a CD with additional labeled images and a link to a website with access to all scanned images. For information contact Dr. Susan Elmore, *elmore@niehs.nih.gov*.

Digital pathology

Digital photo microscopy and slide scanning technologies are now routinely used for NTP and NIEHS studies. They have led to our abilities to publish and present stellar microscopic images, and through web-based telepathology to conduct pathology peer reviews and seek instantaneous opinions from pathologists at remote locations around the world. During the evaluation of an NTP study, pathologists identify representative lesions for photomicroscopy or slide scanning and inclusion in the new pathology database. It is estimated that 70% of the NTP studies require photography, ranging from approximately 5-20 photographs per study. Routinely, the images are used for the Pathology Working Group (PWG) reviews. The NTP, in partnership with NCTR, is currently evaluating the diagnostic quality of digital histopathology by directly comparing the diagnoses given for digital image to the corresponding glass slide. To date, five out of a proposed 10 PWGs have been held and reveal promising results. The establishment of the digital database has led to improved accuracy of pathology diagnoses through peer review of pathology findings, sharing and reporting of pathology data, computerized image analysis, material for publications and monographs, and the generation of teaching material for local, national, and international universities, institutes, and professional meetings/symposia.

During the past decade, the NTP has established and maintained a state-of-the-art approach to capturing and archiving digital images of rodent pathology in a database that has grown to over 60,000 images. The images are primarily obtained by light microscopy but also include electron microscopy as well as magnetic resonance imaging (MRI) and microcomputed tomography (micro-CT). New types of imaging, such as MRI and micro-CT, for both *in vivo* and *ex vivo* studies provide significant increases in data content and efficiency and allow a more complete examination of tissues and organs from animals involved in experimental studies. The images are categorized by species, sex, organ system, treatment, and dose. This work is in direct support of a mission of the NIEHS and the NTP to develop and apply new and improved methods such as medical and scientific imaging to study the adverse effects of environmental factors on human health. Many of the NTP and NIEHS studies employ pathology as the endpoint based on conventional optical microscopy of collected tissue samples.
For information, contact Dr. David Malarkey, *malarkey@niehs.nih.gov.*

Atlas for documenting diagnostic criteria for non-neoplastic lesions

In efforts to standardize and improve the diagnostic accuracy of non-neoplastic lesions in the NTP database, NTP pathologists have been working with contractor pathologists to improve and revised the NTP's Pathology Code Table and nomenclature for non-neoplastic lesions of the mouse and rat. In April 2008, groups of 2-3 pathologists were assigned the task of generating terminology for specific organ systems and then assisting in gathering or generating photomicrographic images of each lesion for the atlas. Lesion thresholds and severity scoring are also being addressed. Dr. Robert Maronpot has been

collecting and organizing the photos and lexicons from each group in order to generate an electronic atlas. Additionally, NTP pathologists are in working groups for the Society of Toxicologic Pathology's International Harmonization of Nomenclature and Diagnostic Criteria committee working towards a worldwide nomenclature standardization of rodent neoplastic and non-neoplastic lesions. The international efforts are relying heavily on NTP expertise and opinion as well as using the NTP's digital database of >60,000 pathology images for examples for the atlases. Some organ systems are complete. For information contact Dr. David Malarkey, *malarkey@niehs.nih.gov*.

Contact Information: Cellular and Molecular Pathology Branch, Dr. Robert C. Sills, Chief, *sills@niehs.nih.gov.*

Genetic and Alternative Test Systems

Host Susceptibility Program

The primary aim of NTP's Host Susceptibility Branch is to develop new models and protocols for hazard identification and risk assessment that are based upon observed differences in the variable range of individual susceptibility to toxicity and disease. Individual genetic differences harbored within the human population are believed to be the basis for individual susceptibility to environmental stressors, including idiosyncratic drug toxicities. At present, environmental and drug safety assessment models use a very limited set of genetic models, which are insufficient to evaluate the influence of individual genetic differences on chemical and drug toxicity.

The aim of this research and testing program is to model the significant genetic diversity in the human population. To meet this aim, the HSB is (1) planning, conducting, and analyzing research on chemical toxicity using multiple, genetically-defined and/or genetically-modified animal models and (2) developing the research base for internal and external research collaborations to promote investigation of the genetic basis for individual differences in susceptibility. A goal is to identity the quantitative trait loci by haplotype-phenotype segregation analysis and conduct functional validation of the candidate genes and their allelic variants that modify individual response to chemical exposure and disease. This information can be used to identify the key genes and pathways involved in response to chemical exposures of presumed or known risk to humans. The use of bioinformatics and comparative genetic analysis and identification of human orthologs will aid the extrapolation between animal models and human toxicity and disease.

Research Currently In Progress:

1. Evaluation of absorption, distribution, metabolism, and elimination (ADME), genotoxicity, and hematotoxicity in multiple inbred mouse strains exposed to low doses of benzene, a model human toxicant, and carcinogen.
2. Genetic analysis of ephedra/caffeine or bis(2-chloroethoxy)methane-induced cardiotoxicity in multiple inbred mouse strains.
3. Short-term cancer bioassays in seven F1 hybrid p53 haploinsufficient haplotyped strains to determine genetic susceptibility to ionizing radiation-induced DNA double strand breaks and tumorigenesis.

Planned Research:

1. Creation and high throughput testing of multiple mouse lymphoblast cell lines (LBCL) using the human CR2 receptor and Epstein-Barr Virus infection for comparative genetics/genomic analysis against human LBCL.
2. Aging and disease phenotypes in multiple inbred mouse strains for development of biomarkers and histopathology indices for aging and disease incidence under NTP control conditions.

3. Development of a whole genome genetically defined, outbred mouse stock created from the G2:F10 generation of 8 parental inbred strains with allelic diversity that exceeds the human population. This stock (at the Jackson Laboratory) is based upon a statistical program that randomly selects breeding (panmixia) and will provide genome-wide allelic diversity exceeding that of the human genome. Protocols for evaluating this stock for toxicology and carcinogenesis studies is under development.

NTP Mouse Sequencing Project

To complement and support the NTP testing program, NTP contracted with Perlegen Sciences, Inc. to identify DNA single nucleotide polymorphisms (SNPs) in 15 commonly used strains of inbred laboratory mice. Using high-density oligonuclueotide array technology, the study identified over 8 million SNPs and other genetic differences between these strains and the previously sequenced C57BL/6J reference strains (Phase 1). By leveraging data provided by the Broad Institute, genotypes were also predicted for 40 other common strains (Phase 2), which were then combined with a novel imputation method to predict the 8 million genotypes in 94 strains. The results of this project presently comprise the world's largest and most accurate resource describing genetic variation in the mouse. The project provides an important experimental resource for gaining improved fundamental understanding of medically important, environmentally related, complex diseases such as cancer and the genetic factors that influence resistance and susceptibility to such diseases. The NTP/Perlegen can be contacted at *http://www.mouse@perlegen.com*.

Contact Information: Host Susceptibility Branch, Dr. John (Jef) French, Acting Chief, *french@niehs.nih.gov.*

Non-mammalian models

The NTP is currently evaluating *Caenorhabditis elegans* (*C. elegans*) as a study organism for assessing the effects of potential developmental and neurological toxicants on multi-cellular organisms. *C. elegans* is a nematode or roundworm about 1 mm in length that lives freely in soil and feeds on bacteria. The use of *C. elegans* is consistent with NTP's strategy to reduce the number of mammals used in testing. Several toxicology assays for feeding, growth, reproduction, and movement have been developed. Table 36 lists *C. elegans* studies ongoing and completed in FY 2008.

Contact Information: Johnathan Freedman, *freedma1@niehs.nih.gov.*

Table 36: Ongoing and Completed *C. Elegans* Studies During FY 2008

Chemical	[CASRN]
Aflatoxin-B1	[1162-65-8]
5,6-Benzoflavone	[6051-87-2]
Benzo(a)pyrene	[50-32-8]
Chlorpyrifos (Dursban)	[2921-88-2]
Ionic liquid (1-butyl-3-methylimidazolium chloride)	[79917-90-1]
Ionic liquid (1-butyl-1-methylpyrrolidinium chloride)	[479500-35-1]
Ionic liquid (*n*-butylpyridinium chloride)	[1124-64-7]
Ionic liquid (1-ethyl-3-methylimidazolium chloride)	[65039-09-0]
Mercuric chloride	[7487-94-7]
Silver nitrate	[7761-88-8]
Sodium selenite	[10102-18-8]

Biomolecular Screening

NTP has established a HTS Program, representing a new paradigm in toxicological testing. NTP is using this HTS approach to screen for mechanistic targets active within cellular pathways critical to carcinogenicity, reproductive and developmental toxicity, genotoxicity, neurotoxicity, and immunotoxicity. NTP's HTS Program is administered through the newly created Biomolecular Screening Branch.

The goals of the HTS Program are three-fold:

1. To prioritize substances for further in-depth toxicological evaluation (to judiciously allocate efforts and resources to maximize public health impact)

2. To identify mechanisms of action for further investigation (e.g., disease-associated pathways)

3. To develop predictive models for *in vivo* biological response (predictive toxicology)

Much of the research conducted in support of the HTS Program will be coordinated with the EPA and the National Human Genome Research Institute (NHGRI) through a Memorandum of Understanding (see page 51).

NTP hosted a Request for Information meeting September 11-12, 2008, at NIEHS. The purpose of the meeting was to obtain information on (1) critical toxicity pathways and useful molecular targets, and (2) technologies and assay systems that might be used in the development of a comprehensive approach to biomolecular screening. The meeting, chaired by Kristine Witt, included presentations on new methods and targets by representatives from 26 scientific organizations.

Contact Information: Biomolecular Screening Branch, Dr. Raymond Tice, Acting Chief, *tice@niehs.nih.gov*.
HTS website: *http://ntp.niehs.nih.gov/go/28213*.

Toxicogenomics Studies

Toxicogenomics studies have been completed on a number of allylbenzne and propenylbenzene class flavor constituents (Table 37).

Table 37: Toxicogenomics studies

Chemical	[CASRN]	Species/Strain	Study Route	Length	Project Leader
Methyleugenol	[93-15-2]	Rats: F344/NTAC	Gavage	90 days	Irwin
Eugenol	[97-53-0]	Rats: F344/NTAC	Gavage	90 days	Irwin
Isoeugenol	[97-54-1]	Rats: F344/NTAC	Gavage	90 days	Irwin
Safrole	[94-59-7]	Rats: F344/NTAC	Gavage	90 days	Irwin
Estragole	[140-67-0]	Rats: F344/NTAC	Gavage	90 days	Irwin
Myristicin	[607-91-0]	Rats: F344/NTAC	Gavage	90 days	Irwin
Anethole	[104-46-1]	Rats: F344/NTAC	Gavage	90 days	Irwin
Isosafrole	[120-58-1]	Rats: F344/NTAC	Gavage	90 days	Irwin

Genetic Alterations in Cancer Database

The NTP Genetic Alterations in Cancer (GAC) knowledge system selects, compiles, and summarizes data reported in the published literature on genetic changes in cancer. The GAC database is unique in that it catalogs mutations by species, target organ, and exposure including chemical, physical, and biological agents. Comprehensive data on alterations (mutations, loss of heterozygosity, and/or specific chromosome changes) in genes implicated in the development of cancers that are associated with environmental exposures are included in GAC and it is the only publicly available knowledge system with such data for both human and rodent neoplasms. GAC currently contains data for 34 cancer genes, 98 chemicals, 12 non-chemical agents, and ~30 major tumor sites.

Data query features retrieve and summarize results from studies of human, mouse, or rat tumors that have data features in common (e.g., topography, genes studied, exposure) to allow relationships between specific genetic changes and cancer types to be assessed. Query results from multiple studies are presented in graphs and tables to facilitate the analysis of the prevalence and spectrum of cancer-specific gene alterations. This aids in evaluating putative mechanisms of tumor development and the role of known environmental factors. The information could be used to promote understanding of the carcinogenic process, and, thus, leverage that knowledge to develop disease prevention strategies, identify specific gene targets, and develop biomarkers for cancer.

In FY 2008, US and international scientists from government, academia, and industry used GAC to investigate gene mutations in cancer. During this period of time the GAC database website received ~ 9000 successful requests for information. Some accomplishments for FY 2008 include: (1) addition of information from over 900 papers added to GAC, (2) data from studies of chromosome loss of heterozygosity were extracted, entered, and checked for quality control, (3) two new programs were released with features for data mining that augment the mutation incidence queries, and (4) the GAC knowledge system was publicized to the scientific community via presentations at two national scientific meetings, American Association for Cancer Research and the Society of Toxicology.

Contact Information:, Dr. June Dunnick, *dunnickj@niehs.nih.gov.*
GAC website: *http://www.niehs.nih.gov/research/resources/databases/gac/index.cfm*

NTP Postdoctoral Training Program

Toxicology and Carcinogenesis

Trainees in this program learn to perform all aspects of contracted toxicology studies for carcinogenic or non-carcinogenic endpoints (e.g., reproductive and developmental effects, immune system function). They learn about NTP efforts in molecular toxicology and HTS and receive training applicable to regulatory or industrial toxicology. By serving as study scientists in non-laboratory positions, they will evaluate the toxicity of substances of interest to the NTP. They actively participate in the design, conduct, and evaluation of studies and have extensive interaction with staff from scientific disciplines such as chemistry, pathology, toxicokinetics, toxicogenomics, genetics, epidemiology, statistics, and molecular biology. Three postdoctoral fellows are currently in the program, Drs. Matt Stout, Scott Auerbach, and Chad Blystone. Collectively in 2008, they published six articles in the peer-reviewed literature and were authors or co-authors on seven abstracts at scientific meetings. All three fellows made research presentations to the NTP Board of Scientific Counselors in 2008 including one carcinogenicity technical report as study scientist (Dr. Stout). In addition, Dr Auerbach was awarded the second place prize in the North Carolina Society of Toxicology PARC awards in 2008. For information contact Dr. Paul Foster, *foster2@niehs.nih.gov*.

Laboratory Animal Medicine

The four-year laboratory animal medicine training program includes clinical and surgical responsibilities, animal care facility management, participation in research projects, and laboratory animal pathology and is a collaborative effort between NIEHS and the University of North Carolina at Chapel Hill. Two postdoctoral fellows are currently in the program, Dr. Jacquelyn Tubbs whose expected completion date is September 2010, and Dr. Coralie Zegre-Cannon, who will finish the program in September 2011. Fellows interact with laboratory animal veterinarians at NIEHS and at local area academic, industrial, and government facilities to received didactic and hands-on training. For information contact Dr. Angela King-Herbert, *kingher1@niehs.nih.gov*.

Toxicological Pathology

Since formalizing a training program in toxicological pathology in 2003, Dr. David Malarkey, training coordinator, and other CMPB staff have mentored eight post-doctoral fellows and over 20 veterinary student externs. Two post-doctoral fellows and four veterinary students participated in the program during 2008. The program is designed to introduce students to the field and career opportunities in veterinary and toxicological pathology while also providing hands-on projects often leading to abstracts and publications. Post-doctoral fellows learn rodent and toxicological pathology, participate in NTP and other DIR research projects, work to achieve accuracy of NTP pathology data by assisting the NTP pathologist on NTP studies, and continue education towards achievement of board certification by the American College of Veterinary Pathologists (ACVP). During 2008, two fellows (Drs. Bhanu Singh and Rebecca Moore) passed the ACVP certifying exam and one (Dr. Deepa Rao) began the program. For information contact Dr. David Malarkey, *malarkey@niehs.nih.gov*.

Information about the NTP Postdoctoral Training Program is available at *http://ntp.niehs.nih.gov/go/33381*.

Interagency Agreements

NIEHS/NCTR Interagency Agreement

NIEHS and FDA have had an IAG in place since 1992, for allowing productive collaborations on studies involving AIDS drugs, dietary supplements, endocrine disruptors, food contaminants, pediatric agents, phototoxic agents, and nanoscale materials. Through the IAG, the NIEHS supports toxicology studies on FDA-regulated agents nominated to the NTP, that are conducted primarily at NCTR Table 38 lists IAG projects completed or ongoing in FY 2008.

Table 38: NIEHS/NCTR Interagency Agreement Projects FY 2008

Study [CASRN] [Principal Investigator]	Objective and/or Rationale
para-Nonylphenol: Evaluation of Reproductive Effects over Multiple Generations [84852-15-3] *[Delclos]*	(1) To determine the effects of *p*-nonyphenol, an intermediate in the production of surfactants and other industrial products, on reproduction and on the development of reproductive and other hormone-sensitive organs when administered to CD rats over five generations; (2) to determine if subtle effects observed in the dose-range-finding study are magnified through multiple generations; and (3) to evaluate the reversibility of any observed effects.
Ethinyl Estradiol: Evaluation of Reproductive Effects over Multiple Generations and the Chronic Effects of Exposure During Various Life Stages [57-63-6] *[Delclos]*	(1) To evaluate the effects of ethinyl estradiol, a potent synthetic estrogen widely used in prescription drugs, on reproduction and on the development of reproductive and other hormone-sensitive organs when administered to CD rats in the diet over five generations; (2) to determine if subtle effects observed in the dose-range-finding study are magnified through multiple generations; (3) to evaluate the reversibility of any observed effects, and (4) to evaluate the chronic toxicity of ethinyl estradiol, particularly the potential induction of cancer of the reproductive organs, following exposure that includes various life stages.
Perinatal Carcinogenicity of Drug Combinations Used to Prevent Mother-to-Child Transmissions of HIV [30616-87-1], [134678-17-4] *[Beland]*	To determine the carcinogenicity, genotoxicity, and metabolism of antiretroviral drug combinations administered to mice transplacentally, perinatally, or neonatally.
Methods Development for Isolating and Detecting Retinyl Palmitate. Effect of Topically Applied Skin Creams Containing Retinyl Palmitate on the Photocarcinogenicity of Simulated Solar Light in SKH-1 Mice. [79-81-2] *[Boudreau]*	To study the effects of topically applied skin cream containing retinyl palmitate on the photocarcinogenicity of simulated-solar light in SKH-1 mice.
Effects of *Aloe vera* Components on Cell Proliferation and DNA Adduct Formation in SKH-1 Mice Following Simulated Solar Light Exposure [8001-97-6] *[Boudreau]*	(1) To determine dose response effects of *Aloe vera* components on edema and cell proliferation in the skin, and (2) to determine if the constituents of *Aloe vera* promote or inhibit the development of skin cancer when the animals are exposed to simulated solar sunlight. The study includes exposures for up to 40 weeks of three *Aloe vera* components, including *Aloe vera* gel, *Aloe vera* whole leaf extract, and charcoal-filtered ("decolorized") *Aloe vera* whole leaf juice.
Aloe vera – Preliminary studies Bioassays in the F-344 Rat and B6C3F1 Mouse Administered *Aloe vera* Plant Constituents in the Drinking Water. *[Boudreau]*	To conduct bioassays in rats and mice using standardized prepara tions of *Aloe vera* to explore the limits of safety for the *Aloe vera* leaf constituents present in commercial products. The use of *Aloe vera* is not limited to over-the-counter dermal therapeutics and cosmetics. *Aloe vera* is also taken internally, and *Aloe vera* for internal consumption is also widely used as a prophylaxis and treatment for a variety of unrelated systemic conditions.

Study [CASRN] [Principal Investigator]	Objective and/or Rationale
Genotoxicity, Mutagenicity and Exposure Biomarkers of Acrylamide and Its Metabolite Glycidamide in Rodents. [79-06-1], [5694-00-8], *[Doerge]*	(1) To synthesize chemically and characterize spectroscopically the major glycidamide-DNA adducts; (2) to develop and validate LC-ES/MS/MS assays to quantify the major glycidamide-DNA adducts; (3) to determine glycidamide-DNA-adduct levels in rodent tissues following short-term exposures of rodents to acrylamide and to glycidamide; (4) to determine toxicokinetics and compare bioavailability of acrylamide and glycidamide following exposure by intravenous, oral gavage, and dietary administration; (5) to correlate the levels and kinetics of glycidamide-DNA adduct in target tissues and circulating lymphocytes with acrylamide- and glycidamide-hemoglobin adducts in rodent exposure studies for future use in monitoring human exposure through occupation, smoking, and diet; (6) to determine mutagenicity of acrylamide and glycidamide *in vivo* using transgenic Big Blue mice; (7) to measure rat and mouse urinary metabolites from acrylamide dosing by IV, gavage and dietary administration to complete the PBPK model; and (8) to investigate the possible affect of acrylamide treatment on neuroendocrine processes with regard to carcinogenicity and neurotoxicity using hormone measurements in conjunction with histopathological, neurochemical, genomic and metabonomic investigations of rats dosed with acryamide.
Study of Toxicity of AIDS Therapeutics in p53 (+/-) and p16/p19 (+/-) Transgenic Mice (AZT, 3TC and NFV Alone and in Combination). [30616-87-1], [134678-17-4] *[Leakey]*	To evaluate the potential toxicity and carcinogenicity of perinatal and chronic exposures to AIDS drugs, Zidovudine (AZT) and Lamivudine (3TC) in C57BL/6(N5)trp53 (+/-) haplodeficient F1 transgenic mice.
Genotoxicity and Carcinogenicity of Acrylamide and its Metabolite Glycidamide in Rodents [79-06-1], [5694-00-8] *[Beland]*	To compare the carcinogenicity of acrylamide and its metabolite glycidamide in B6C3F1 mice and F344 rats treated chronically for two years.
N-Methyl-D-aspartic acid (NMDA) Antagonist/ Gamma-Aminobutyric Acid (GABA) Agonist-induced Cell Death in the Developing Rat Brain [1867-66-9] *[Wang, Slikker]*	To screen and evaluate pediatric anesthetic agents (NMDA antagonists/GABA agonists).
Nanoscale Material Toxicology: Quantum Dots (Qdots) TiO_2. [1317-70-0] [Howard]	To investigate the penetration of quantum dots into the skin of SKH-1 mice.
Developmental Neurotoxicity Assessment of Acrylamide in Rats: Long- term Studies [79-06-01] / *[Paule]*	To determine the consequences of long-term exposure to acrylamide on a variety of developmental milestones and measures of nervous system integrity throughout life.
Tumorigenicity of Photoactive Nanoscale TiO_2 in Tg-AC Transgenic Mice. [1317-80-2] *[Howard]*	(1) To determine if topical application of nanoscale TiO_2 results in penetration of the TiO_2 into the hair follicle of FVB/N mice; (2) to determine the dose-response relationship of follicular penetration by TiO_2; (3) to repeat the UVB doses used in the Trempus *et al*., 1998, study to confirm reproducibility of the UVB dose that is photocarcinogenic; and (4) to dose mice with a high dose of UVA to determine photocarcinogenicity.
Range Finding Study on Toxicity of Usnic Acid and *Usnea* sp lichen. [125-46-2], [84696-53-7] *[Leakey]*	To establish appropriate doses of usnic acid and *Usnea barbata* preparations administered in feed to male and female Fischer 344 rats and B6C3F1 mice for use in subsequent subchronic and chronic studies.
Subchronic Toxicity Studies of Glucosamine and Glucosamine Chondroitin Sulfate Combinations in Obese and Lean Zucker Rats. [3416-24-8], [9007-28-7] *[Leakey]*	(1) To investigate the potential toxicity of chondroitin sulfate and glucosamine, administered by oral gavage in male rats, and (2) to determine whether subchronic exposure of glucosamine or chondroitin sulfate potentiate the pathological effects of noninsulin-dependent.

Study [CASRN] [Principal Investigator]	Objective and/or Rationale
DEHP Toxicokinetics in Neonatal Male Rhesus Monkeys Following Intravenous and Oral Dosing. [117-81-7] *[Delcos]*	(1) To quantify the metabolism and disposition of multiple, single-intravenous doses of DEHP administered to male rhesus monkeys during the first 12 postnatal weeks; (2) to quantify the metabolism and disposition of multiple, single-oral doses of DEHP administered to male rhesus monkeys during the first 12 postnatal weeks; (3) to evaluate the feasibility and utility of a subchronic toxicity study of DEHP using repeated IV exposures in neonatal rhesus monkeys; and (4) to utilize blood and testicular tissue from infant monkeys to establish methods to be utilized in the subchronic study and/or estimate variability in the endpoints to aid in determining the number of animals required in each dose group for a subchronic study.
The Immunogenicity of Permanent Makeup Inks and Their Components. *[Howard]*	To determine the immunogenicity of permanent make-up inks using a modified lymph node proliferation protocol.
Effects of Sedatives on he Metabolism of DEHP Administered by IV Injection and the Relationship of DEHP Metabolism to Biological Effects in Neonatal Rats. [117-81-7] *[Delcos]*	To investigate the metabolic consequences of sedation with ketamine and isoflurane on the metabolism of intravenously administered DEPH in Fischer 344 neonatal rats.
Maintenance of the Transgenic p16/p19(-/+) Haplodeficient [NCTR strain code, 7V] Breeding Colony for Subsequent NTP Protocol Development. *[Lewis]*	To maintain the NCTR p16/p19 breeding colony for the development of a strain of haplodeficient mice that could be used in GMM 9-month studies for rapid drug evaluation for carcinogenesis.
Determination of Carcinogenic Mechanisms for Furan in Male Fischer 344 Rats. [110-00-9] *[Doerge]*	To determine the pharmacokinetic mechanisms, mutagenesis and hepatotoxicity of low doses of the carcinogen furan in rodents.
Subchronic Toxicology Studies of Usnic Acid in Fischer 344 Rats and B6C3F1 Mice. [125-56-2] *[Leakey]*	To determine the toxicity of orally administered usnic acid, the active ingredient in *Usnea* products.
Subchronic Toxicology Studies of *Usnea lichen* in Fischer 344 Rats and B6C3F1 Mice. [84696-53-7] *[Leakey]*	To determine the toxicity of *Usnea* lichen, administered orally.
Physiological Effects of Bitter Orange in Rats. [94-07-5] *[Hansen]*	To determine potential physiological effects of synthetic synephrine as well as an extract from the botanical citrus aurantium alone and in combination with caffeine in rats.
To Determine Potential and Developmental Toxicity of Synthetic Synephrine and Citrus Aurantium Extract in Rats. [94-07-5] *[Hansen]*	To determine potential developmental toxicity of synthetic synephrine citrus aurantium extract in rats.

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NIEHS/NIOSH IAG – Comprehensive Assessment of Occupationally-Relevant Exposures

The NTP is coordinating an effort with NIOSH to better understand worker exposures, identify occupational health research gaps, and educate workers. Current efforts listed in Table 39 are addressing worker exposure to welding fumes, abrasive blasting materials, metalworking fluids, tungsten oxide fibers, and nano-sized materials.

Table 39: NIEHS/NIOSH Interagency Agreement on Occupationally Relevant Exposures FY 2008

Task Order [Project Officer]	Objective and/or Rationale
Administrative Support/ *[Toraason]*	NIOSH scientists participate in (1) review and oversight of NTP activities and (2) several NTP meetings held in Research Triangle Park, NC; Washington, DC; Morgantown, WV; and Seattle, WA.
Tungsten Oxide Fiber Dissolution and Persistence in Artificial Human Lung Fluids *[Stefaniak]*	(1) To characterized five tungsten oxide (WO3.00, WO2.98, WO2.81, WO2.66, WO2.51) powders and (2) to determine the relative solubility of tungsten oxide powder materials in artificial human extracellular lung fluid and of tungsten oxide fibers in artificial human lung macrophage phagolysosomal fluid.
Exposure Assessment in Domestic Tungsten Refining and Manufacturing Occupations *[McKernan]*	(1) To identify airborne fibers in tungsten manufacturing industries; (2) to utilize a method to count and qualitatively determine elemental constituents of the fibers; and (3) to investigate the presence of airborne tungsten containing fibers in down-stream consumers, manufacturers, and industrial users that consume or incorporate tungsten in their products.
Assessing the Feasibility of Industry-wide Exposure and Epidemiology Studies of Workers Exposed to Engineered Nanomaterials *[Schubauer-Berigan]*	(1) To collect and compile information on the size, characteristics and future trends of the US workforce involved in the manufacture of engineered carbonaceous nanomaterials; and (2) to identify companies to be profiled in a report on the feasibility of conducting industry-wide exposure surveys and epidemiologic studies among this workforce. NIOSH will use the contractor Battelle for assistance with this study.

NTP/NIOSH IAG – Immuntoxicology

The goal of this IAG is to provide support of NTP hazard identification activities targeted toward the prevention of diseases or adverse effects caused by environmental exposure to chemical or physical agents. These cooperative studies continue to improve the risk assessment process by determining quantitatively what constitutes an adverse health effect on the immune system in humans. These studies, listed in Table 40, evaluate unique cohorts of individuals from professions associated with immune-mediated occupational diseases including asthma, contact dermatitis, allergy to mold spores, chronic beryllium disease, allergic rhinitis, silicosis and latex allergy. These cohorts are being studied for a number of endpoints including impact of genetic polymorphisms on inflammatory disease development and clinical outcomes and identification of unique immunological biomarkers for disease. The NIOSH Laboratory for Occupational Genomics serves as a resource for obtaining samples from individuals with occupational and occupationally related diseases.

Table 40: Immuntoxicology Studies FY 2008

Study [Principal Investigator]	Objective and/or Rationale
Chronic sinusitis and mold exposure *[Beezhold]*	To investigate of the role of fungi in chronic sinusitis.
Heading off Environmental Asthma in Louisiana *[Beezhold]*	To assess total IgE and mold specific IgE in asthmatic children in post-Katrina The study is in collaboration with Tulane University.
NIEHS Agricultural Pesticide Study *[Beezhold]*	(1) To evaluate allergic sensitization in a cohort of sera from 700 farmers with or without pesticide exposures, and (2) to assay for deoxinivinol (a potential biomarker for occupational exposures) levels in the serum.
Role of Genetic Variation in Environmental and Occupational Diseases – Irritant Dermatitis Genetics *[Yucesoy]*	(1) To test the hypothesis that individuals with increased susceptibility to occupational irritants express a certain genetic pattern and that this pattern is associated with polymorphisms in genes that control immune and inflammatory responses, and (2) to support purchase of gene platforms as well as funds research collaborators for subject compensation. This study is in collaboration with Case Western Reserve and West Virginia University School of Medicine.
Role of Genetic Variation in Environmental and Occupational Diseases – Occupational Asthma *[Yucesoy]*	To investigate the association between functional polymorphisms within cytokine, inflammatory, antioxidant, and major histocompatibility complex genes and the occurrence and clinical outcomes of asthma, gene-gene/ gene-environment interactions, and (2) to study single nucleotide polymorphisms the major histocompatibility complex region.
Investigations into Health Effects Caused by Exposure to Indoor Air Reaction Products (supportive animal studies) *[Wells, Anderson]*	(1) To identify and quantify the reaction products of gas-phase compounds present in the indoor environment, especially dicarbonyls; (2) to investigate the immunotoxic effects of these reaction products; (3) to identify biomarkers can be used to screen indoor environments; and (4) to complete both *in vitro* and *in vivo* assays to assess adverse health effects caused by exposure to indoor air reaction products.

Study [Principal Investigator]	Objective and/or Rationale
Immunological Mechanisms of Occupational Rhinitis Induced by Diisocyanate Exposure (supportive animal studies and field studies) [Johnson]	(1) To diagnose and collect samples from workers from Canada and Spain exposed to diisocyanates; (2) to clinically characterize upper and lower airway disease, as well as specific inhalation challenge with the suspected diisocyanate compound; and (3) to gain an understanding of the pathobiology of occupational rhinitis which may lead to the identification of biomarkers useful in earlier diagnosis of disease.
Toluene Diisocyanate (TDI) Monoclonal Antibody Production and Characterization (improved methods) [Siegel]	(1) To produce and characterize of 35 monoclonal antibodies against 2,4-TDI protein and 13 monoclonal antibodies against 2,6-TDI-protein; (2) to complete characterization of all monoclonal antibodies, especially with respect to minimal epitope required for reactivity of the monoclonal antibodies to a TDI-reacted chemical; and (3) to examine the utility of select monoclonal antibodies for immunoassay, immunohistochemistry, and proteomic analyses of tissues following TDI exposure.
Determination of Total IgE, Antinuclear Antibodies and Atopy In Plasma From Members of Upper Midwest Health Study, A Case-Control Study of Intracranial Gliomas (field study) [Biagini]	To assess members of the Upper Midwest Health Study (1) to determine total IgE, antinuclear antibodies, and atopy in plasma, and (2) to test for common allergies.
Antibody Levels in Systemic Lupus Erythematosus (field study) [Biagini]	To measure total serum IgA, IgM and IgG in sera from systemic lupus erythematosis patients to investigate whether adjustment for total immunoglobulin levels may unmask differences in serum IgE levels.

Appendix I

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